Targeting innovation in antibiotic drug discovery and development

The need for a One Health – One Europe – One World Framework

Matthew J Renwick, Victoria Simpkin and Elias Mossialos

A very thorough analysis of the different initiatives to stimulate research and innovation of antibiotics

Edith Schippers, Minister of Health, Welfare and Sport, The Netherlands

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Targeting innovation in antibiotic drug discovery and development

The need for a One Health – One Europe – One World Framework

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Foreword

Ms Edith Schippers
Minster of Health, Welfare and Sport
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Resistance to available antibiotics is one of the biggest threats to public health and our healthcare systems. Bacteria and infections that we cannot treat anymore, the medical procedures that cannot be performed anymore without life-threatening risks… the consequences of antibiotic resistance are beyond our imagination. That is why I have put antibiotic resistance high on the agenda of the Dutch Presidency and why I want to continue to call for action in other international forums.

I believe in a One Health approach to this complex problem. It is a challenge we can only tackle by joining forces with multiple disciplines, by different solutions and new ideas. In the Netherlands we believe that working together in a One Health approach is crucial. This means closer collaboration between the human and veterinary side and between the different research instruments that we have. In February this year, The Netherlands Organisation for Health Research and Development launched a new €16 million research programme on antibiotic resistance, based on the One Health approach.

One important solution set is the development of new antibiotics that are, ideally, less sensitive to resistance, alternative treatment and prevention options such as vaccines, and rapid diagnostics to target therapies. Scientists from different research areas, from academia and industry, from different countries, already work together in various research initiatives to develop these new ways to combat bacterial infections. It is important that they keep working together, share knowledge, define a shared strategic research agenda that reflects public health needs and urgent threats. By a close connection to public health needs and shared strategy and choices, we can avoid duplicating efforts and seek collaboration.

The London School of Economics conducted a very thorough analysis on the different initiatives already in place to stimulate research and innovation of antibiotics, alternative strategies and diagnostics. This study is very useful as it gives detailed insight into the scope and focus of all important initiatives, and an overview of the research field. It is interesting that the London School of Economics found an imbalance towards push incentive tools in the current initiatives, and an unequal distribution of initiatives across the antibiotic value chain. These findings provided pivotal input for the Minsterial Conference on AMR on February 9th, in Amsterdam. I hope they will add to future discussions on global research on AMR and business models for new antibiotics.

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Executive Summary

Antimicrobial resistance is currently responsible for over 700,000 deaths annually around the world. AMR mortality is predicted to exponentially rise to above 10 million deaths per year by 2050. The global economic cost of such a rise in mortality and morbidity is estimated to be $100 trillion.

Development of novel antibiotics, alternative therapies and diagnostics tools is critical to the global fight against AMR. However, the pipeline for antibiotics and related products is limited. Since 2000, only five novel classes of antibiotics have been marketed, however none of these target deadly and highly resistant gram-negative bacteria. The total number of submitted antibiotic patents has declined by 34.8% between 2007 and 2012.

A partial picture of the EU/US antibiotic pipeline shows that there are at least 19 antibiotic products including alternative therapies in clinical development Phase I, 27 in Phase II and 6 in Phase III. Despite 52 products in the pipeline, only one is a systemic antibiotic with a novel mechanism of action and it is limited to a specific bacteria. A development timeline for these drugs is unknown.

A partial picture of US and EU public funding of antibiotic R&D demonstrates that Europe has invested ~€147 million annually between 2007–13 and the US has invested $260 million (€234 million) in 2015. Having been stable since 2010, US investment in antibiotic R&D is expected to grow to $413 million (€382 million) in 2016. However, it is unclear how the differences in funding have affected outcomes in the pipeline, which highlights the need for ongoing assessment of public return on investment in antibiotics. Moreover, European and US governments appear to have only limited means of eventually recapturing these large investments should their funding result in marketable antibiotics.

Regarding private investment, global venture capital in antimicrobial R&D has declined by 28% between the two five year periods of 2004–08 and 2009–13. Venture capital investment in gram-negative antimicrobials has increased by 51% during these two periods, but it still comprises only 12% of total venture capital investment in antimicrobials. The amount of internal capital invested by developers into their own antibiotic projects is unknown.

In response to this growing crisis, there has been a proliferation of initiatives to incentivize the antibiotic development pipeline. In total, there are 58 active R&D initiatives and sub-initiatives at global, EU and national levels (UK, France, Germany, Netherlands, Sweden, US and Canada) that directly incentivize antibiotic R&D. Additionally, there are nine active initiatives that indirectly support antibiotic R&D by coordinating strategic actions on AMR and seven initiatives that are either proposed or in preliminary stages of implementation.

The antibiotic R&D initiative environment is now crowded. There is room for improved coordination both between and within initiatives. Many initiatives are founded on various models of partnership that improve the possibilities for stakeholder collaboration but further complicate coordination efforts. A lack of coherence throughout R&D initiatives risks muddling priorities, duplicating efforts and missing synergistic opportunities.

Most initiatives improve the economic value of antibiotic R&D, but there is a heavy imbalance towards the use of push incentive tools. Of the active initiatives, 76% use only push mechanisms, 5% use only outcome-based pull mechanisms, 5% use lego-regulatory policies and 13% only coordinate AMR action and provide no form of R&D incentive. Only one initiative, the US BARDA, has the capacity to use a hybrid push-pull approach to incentivization. The top three incentives are: direct project funding, research collaborations and research grants and fellowships. The vast majority of funding flows through push mechanisms of incentivization.

Due to this push/pull imbalance, there is an unequal distribution of initiatives across the antibiotic value chain that favours basic research and early drug discovery phases. In addition, R&D initiatives primarily assist academic institutions and large pharmaceutical companies. SMEs are lacking support and often struggle to reach the clinical phases of development and market approval. Taxation policies that can be tailored to support SMEs developing antibiotics do not appear to be commonly used.

At the end of the antibiotic value chain, commercialization-focused pull incentives that are missing or are underutilized include end prizes/competitions and value-based pricing and reimbursement. Moreover, the EMA and FDA are using regulatory tools to facilitate antibiotic market authorization. There is room for further harmonization and cooperation between the EMA and FDA, as well as other drug regulatory agencies.

Finally, from a public health perspective, antibiotic stewardship and patient access goals are poorly integrated into the current set of R&D initiatives. Many initiatives have not explicitly linked their incentives to high-priority medical needs in infectious disease.

Given this research report's key findings, we put forth the following 16 recommendations:

1. Align existing and new antibiotic R&D initiatives to function within the broader One Health approach to AMR.

2. Consolidate and coordinate existing and new European AMR initiatives and antibiotic R&D initiatives under a One Europe approach.

3. Establish a global AMR policy coordination and governing body that brings worldwide coherence under a One World approach.

4. Intensify efforts to coordinate and expand European and global antibiotic clinical trial programmes under One Europe and One World agendas.

5. Ensure antibiotic incentives are explicitly attached to specific high-priority medical needs in infectious disease.

6. Ensure antibiotic incentives reinforce global stewardship and access goals.

7. Link push and pull incentive mechanisms in a hybrid approach to stimulating antibiotic R&D.

8. Launch a global AMR observatory that collects AMR and antibiotic pipeline data, shares knowledge and disseminates best practices in AMR and antibiotic innovation.

9. Establish European and global commitment to antibiotic pull incentives.

10. Explore the role for European joint procurement of high-value antibiotics to ensure their conservation.

11. Consider the feasibility of European tax policies that encourage antibiotic R&D.

12. Incorporate methods of clawing back public investment in antibiotic R&D into incentive packages.

13. Improve cooperation and harmonization across global drug regulatory agencies for licensing novel antibiotics.

14. Address key market weaknesses by further enabling SME participation and facilitating preclinical development.

15. Explore the incentive preferences of different industry players.

16. Investigate the value of different partnership models in antibiotic R&D and learn from the experiences of the BARDA, IMI and JPIAMR.

List of abbreviations

AB	Antibiotic
ABSSSI	Acute bacterial skin and skin structure infection
ACE	Antibiotic Conservation Effectiveness
AHIF	Antibiotic Health Impact Fund
AIDS	Acquired immune deficiency syndrome
AIFM	Antibiotic Innovation Funding Mechanism
AMC	Advanced market commitment
AMR	Antimicrobial resistance
AMRFF	Antimicrobial Resistance Funders Forum
ANR	French National Research Agency
ANTUK	Antibiotic Research UK
ARLG	Antibacterial Resistance Leadership Group
AVIESAN	French National Alliance for Life Sciences and Health
BARDA	Biomedical Advanced Research and Development Authority
BIO	Biotechnology Industry Organization
BMBF	German Federal Ministry for Education and Research
BSA	Broad spectrum antimicrobials
BSAC	British Society of Antimicrobial Chemotherapy
CABP	Community acquired bacterial pneumonia
CDC	US Centers for Disease Control and Prevention
cIAI	Complicated intraabdominal infection
CIHR	Canadian Institutes of Health Research
CIHR-III	Canadian Institutes of Health Research – Institute of Infection and Immunity
COMBACTE	Combating Bacterial Resistance in Europe
COMBACTE-CARE	Combating Bacterial Resistance in Europe – Carbapenem Resistance
COMBACTE-MAGNET	Combating Bacterial Resistance in Europe – Molecules Against Gram-Negative Infections
CTTI	Clinical Trials Transformation Initiative
cUTI	Complicated urinary tract infection
DFG	German Research Foundation

DG RTD	Directorate-General for Research and Innovation
DG SANTE	Directorate-General for Health and Food Safety
DISARM	Developing an Innovative Strategy for Antimicrobial Resistance
DNDi	Drugs for Neglected Diseases Initiative
DZIF	German Centre for Infection Research
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EDCTP	European and Developing Countries Clinical Trials Partnership
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFSA	European Food Safety Authority
EIB	European Investment Bank
EMA	European Medicines Agency
ENABLE	European Gram-Negative Antibacterial Engine
EU	European Union
FDA	US Food and Drug Administration
FNIH	Foundation for National Institutes for Health
FP6	Sixth Framework Programme
FP7	Seventh Framework Programme
GAIN	Generating Antibiotic Incentives Now
GSK	GlaxoSmithKline
GUARD	Global Union for Antibiotics Research and Development Initiative
HAP	Hospital acquired pneumonia
HIT	High intensity throughput
HIV	Human immunodeficiency virus infection
iABC	Inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis
IDSA	Infectious Disease Society of America
IMI	Innovative Medicines Initiative
IMMI	Inserm's Institute for Microbiology and Infectious Diseases
InnovFin ID	InnovFin Infectious Diseases
Inserm	French National Institute of Health and Medical Research

JPIAMR	Joint Programming Initiative on Antimicrobial Resistance
LMIC	Low- and middle-income countries
LPAD	Limited Population Antibacterial Drug
NAA	Novel alternative to antibiotics
ND4BB	New Drugs for Bad Bugs
ND-AB	Neglected and disused antibiotics
NGO	Non-governmental organization
NIAID	National Institute for Allergies and Infectious Diseases
NIH	US National Institutes for Health
NPV	Net present value
OECD	Organisation for Economic Co-operation and Development
OHE	Office of Health Economics
OMA	Options Market for Antibiotics
PDP	Product development partnership
PPP	Public-private partnership
PQP	Prequalification of Medicines Program
QIDP	Qualified Infectious Disease Product
R&D	Research and development
RCT	Randomized controlled trials
ROI	Return on investment
SME	Small and medium sized enterprises
SRC	Swedish Research Council
TATFAR	Transatlantic Task Force on Antimicrobial Resistance
TB	Tuberculosis
UK	United Kingdom
UK-MRC	UK Medical Research Council
UKCRC TIRI	UK Clinical Research Collaboration Translational Infection Research Initiative
US	United States of America
UN	United Nations
WHO	World Health Organization
ZonMw	Netherlands Organisation for Health Research and Development

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1. Objectives

The 2016 Dutch Presidency of the European Union (EU) has named antimicrobial resistance (AMR) a top priority in their upcoming policy agenda and held a Ministerial Conference on this issue in February 2016. In preparation for this conference, the Dutch Ministry of Health, Welfare and Sport commissioned the London School of Economics' health research centre, LSE Health, to submit a report that would provide a platform for discussion among the attending European Ministers of Health and Ministers of Agriculture. More specifically, this report would review current policy instruments aimed at incentivizing the innovation of novel antibiotics, alternative therapies and diagnostic devices that support the rapid assessment of bacterial infections. This report would build on LSE Health's previous research commissioned by the Swedish government.[1] One follow-up implication of this previous report was the establishment of the Transatlantic Taskforce on Antimicrobial Resistance.

Antimicrobial resistance is a complex, multi-factorial problem requiring a global solution that tackles the issue from multiple different angles. One key aspect of a global solution is the development of novel antibiotic drugs to support or replace the increasingly ineffective set of antibiotics currently available. However, the pipeline for antibiotics is limited because there are numerous scientific, regulatory and economic barriers that prevent adequate investment in antibiotic research and development (R&D). In response to this growing crisis, multiple R&D initiatives have been implemented at international, EU and national levels to reinvigorate the antibiotic development pipeline. These are an excellent first step, however, it appears that the current programmes are not sufficient to repair the pipeline; additional intervention is necessary.

The primary objective of this report is to identify gaps in the European R&D agenda for antibiotics, as well as to recommend solutions to identified policy gaps. Through an extensive review of literature and input from experts in the field, we first seek to identify the existing set of initiatives that incentivize R&D of antibiotics and related medical products. We review international and EU R&D initiatives and additionally national programmes in the US, Canada, UK, France, Germany, Sweden and the Netherlands. Following this mapping exercise, we will discuss the most important initiatives and apply an analytical framework to assess these programmes. Finally, based on our research we will identify key policy questions that deserve further discussion. This discussion will ultimately inform our set of policy recommendations on how to improve the European R&D agenda for antibiotics.

2. Background

2.1 Combating the rise of antimicrobial resistance

Antibiotics are essential to modern medical care. They are used routinely as prophylaxis in elective surgeries, as well as lifesaving measures in critically ill patients. However, AMR is a constant threat to antibiotics in the ever-shifting landscape of infectious disease. Microorganisms targeted by antimicrobial drugs evolve and naturally select for immunity to these medical weapons. This process is accelerated by the widespread, and often inappropriate, use of antibiotics in human and veterinary contexts.

AMR has spread so rapidly that it has been identified by the World Health Organization (WHO) as one of the greatest current threats to global health.[2] Numerous lethal pathogens have resistance levels exceeding 25% within EU states and other threatening microorganisms are surpassing 50% resistance rates throughout the world.[2] The recent emergence of MCR-1, a plasmid-mediated colistin resistance mechanism, marks the final breach of antibiotics by plasmid-mediated resistance.[3] Studies conducted by RAND Europe and KPMG for the UK's Review on Antimicrobial Resistance estimated that global antibiotic resistance is responsible for over 700,000 deaths each year.[4] Global deaths due to AMR are predicted to exponentially rise above 10 million deaths per year by 2050 (Figure 1).[4] They further estimate that the economic costs of such a rise in mortality and morbidity would likely be $100 trillion.[5]

A comprehensive strategy is necessary to address the challenges that accompany the rising threat of AMR. The Transatlantic Task Force on Antimicrobial Resistance (TATFAR) outlined three critical tasks that must be undertaken to effectively fight AMR (Figure 2).[6] First, therapeutic use of antibiotics needs to be conducted appropriately in medical and veterinary contexts. Second, drug-resistant infections need to be controlled and prevented. Third, strategies are necessary to preserve existing antibiotics and improve the development pipeline for new antibiotics, alternative therapies and diagnostic devices. A crucial aspect of this third task, and the focus of this report, has been the design and implementation of reforms that facilitate R&D of AMR products.

While not further discussed in this report, preventing the spread of resistance and facilitating appropriate use of antibiotics are being addressed by multiple European directorates and agencies including: the European Commission's (EC) Directorate-General for Health and Food Safety (DG SANTE), the EC's Directorate-General for Research and Innovation (DG RTD), the European Medicines Agency (EMA), the European Food Safety Authority (EFSA) and the European Centre for Disease Prevention and Control (ECDC). A comprehensive mapping and assessment of these public health programmes is a worthy research topic and would aid in the improvement of the European AMR agenda.

Figure 1 Deaths attributable to AMR every year compared to other major causes of death[4]

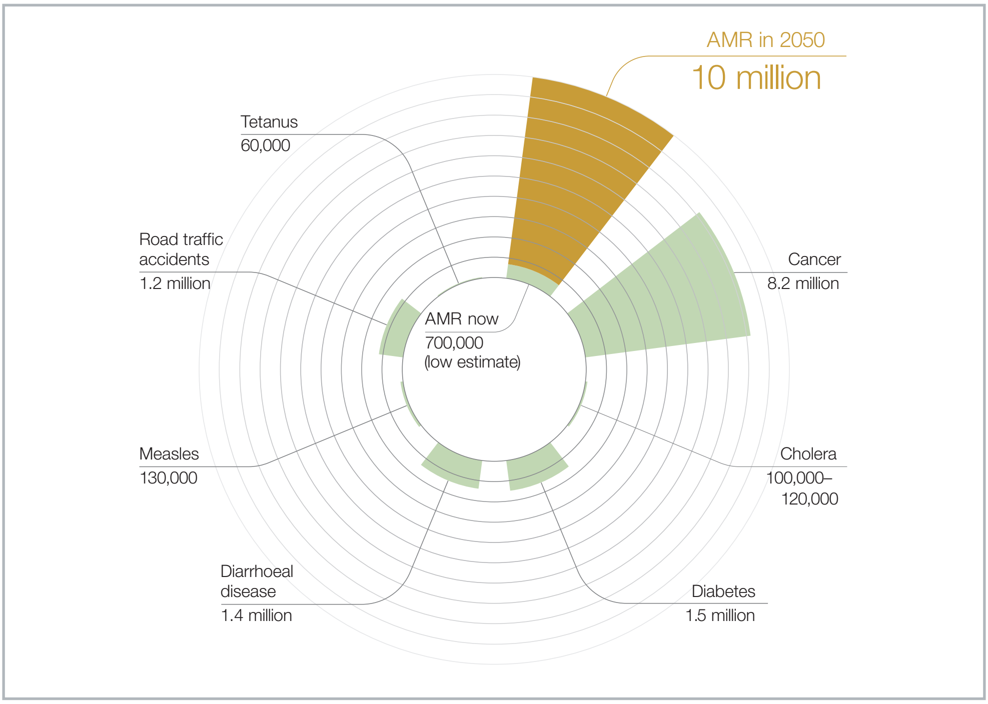
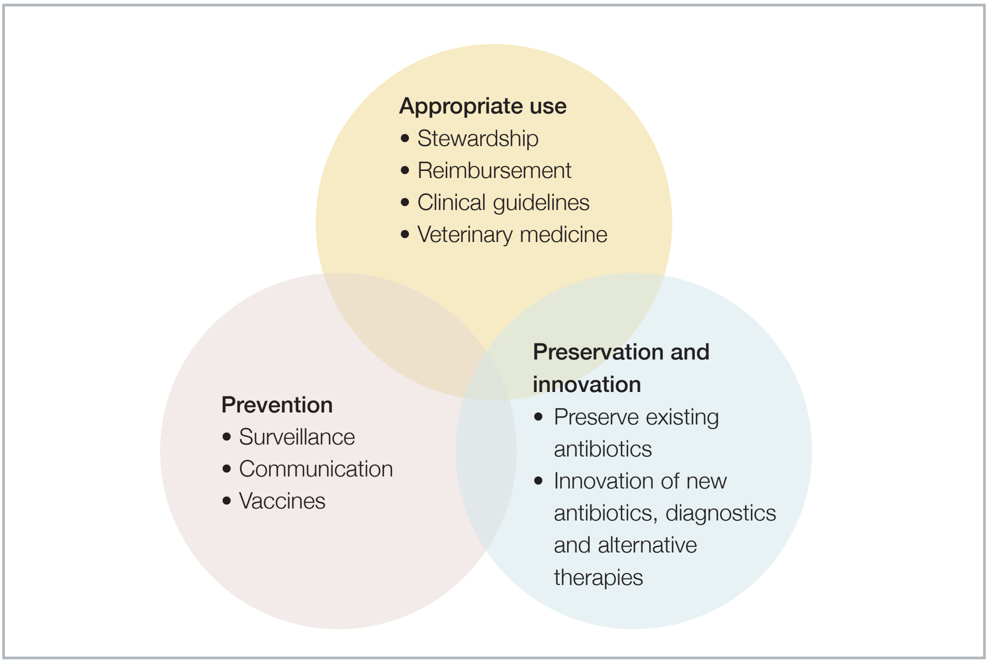


Figure 2 Critical tasks for effectively combating AMR as identified by TATFAR[6]



The terms antimicrobials, antibacterials and antibiotics are different and have specific medical terminology. However, they are often used interchangeably in the literature and by relevant organizations and initiatives. For the purposes of this report they are used interchangeably to refer to natural and synthetic compounds that target various pathogens, including bacteria.

2.2 The lagging antibiotic development pipeline

There is clear demand for new generations of antibiotics to replace the increasingly ineffective ones, however, the development pipeline is strained. Since 2000, only five novel classes of antibiotics have been marketed: oxazolidinones, lipopetides, pleuromutilins, tiacumicins and diarylquinolines (Table 1).[7] A new class of antibiotic is structurally unique and not a derivation of a previous class, thus insusceptible to existing resistance mechanisms.[8] Unfortunately, none of these five new classes target gram-negative bacteria, which are often deadly and known to more readily adapt to antibacterial drugs.[7] The well-known "ESKAPE" pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter*) are gram-negative and cause the majority of hospital acquired infections, yet few drugs in the R&D pipeline target these bacteria.[9]

It would also seem that the development pipeline is not accelerating at the needed rate despite calls to actions, as pharmaceutical companies continue to divest from antibiotics. A life sciences report by Marks & Clerk found that the total number of patent applications worldwide related to antibiotic research has dropped considerably.[10] In 2007, a total of 8,565 antibiotic patents were filed across the globe and in 2012 this number plummeted to 5,586, a 34.8% decrease (Figure 3). In contrast, the number of patent families* in the field of antibiotics filed over the same period stayed quite constant. This combination of decreasing total patent filings and stable patent family filings may be a result of consolidations in antibiotic patent filings or, more worryingly, it may indicate general apathy and uncertainty in antibiotic development.

Currently, GlaxoSmithKline, Novartis, AstraZeneca and Sanofi-Aventis are the major large-capital pharmaceutical companies that are actively developing antibiotics.[7] This number has shrunk significantly since 1990 when there were at least 18 big pharmaceutical companies active in the field.[7] This recent decade has also been a period of substantial commercial restructuring, as many pharmaceutical companies have either established or closed antibiotic R&D subsidiary firms. As a result, small and medium sized enterprises (SMEs) have attempted to fill any void created by the fluidity in the infectious disease sector. This is a trend that is common throughout the pharmaceutical industry. Munos found that, between the early 1980s to early 2000s, the proportion of new drugs attributable to SMEs had increased from 23% to 70%.[11] Regrettably, these SMEs often lack the capital to undertake R&D of novel antibiotics and have resorted to redeveloping

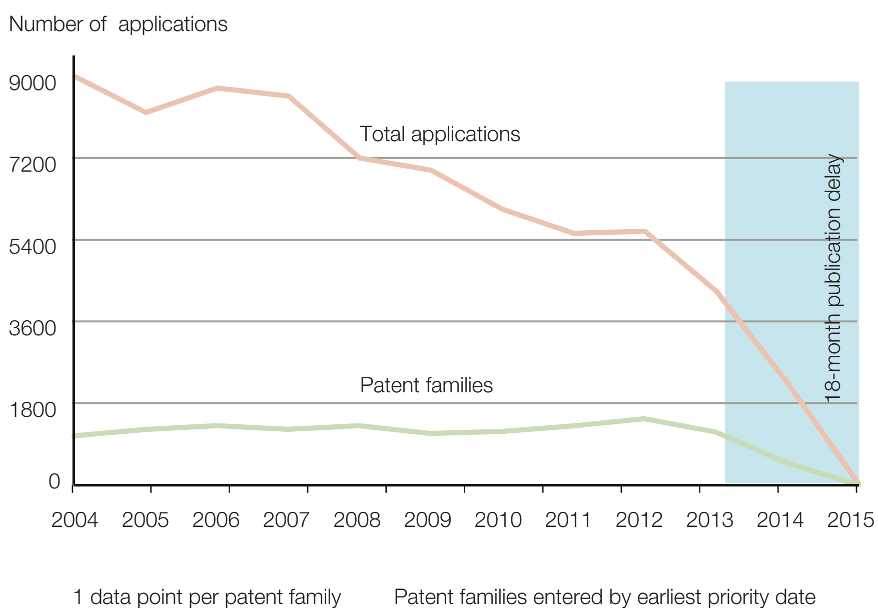
* Patent families are a set of patents covering a single invention.

Table 1 Antibiotic pipeline since 2000[7]

Year approved	Drug name	Class	Bacteria type
2000	Linezolid	Oxazolidinone*	G+ve
2001	Telithromycin	Macrolide	G+ve/G–ve
2002	Biapenem	Carbapenem	G+ve/G–ve
2002	Ertapenem	Carbapenem	G+ve/G–ve
2002	Prulifloxacin	Fluoroquinolone	G+ve/G–ve
2002	Pazufloxacin	Fluoroquinolone	G+ve/G–ve
2002	Balofloxacin	Fluoroquinolone	G+ve/G–ve
2003	Daptomycin	Lipopeptide*	G+ve
2004	Gemifloxacin	Fluoroquinolone	G+ve/G–ve
2005	Doripenem	Carbapenem	G+ve/G–ve
2005	Tigecycline	Tetracycline	G+ve/G–ve
2007	Retapamulin	Pleuromutilin*	G+ve
2007	Garenoxacin	Quinolone	G+ve/G–ve
2008	Ceftobiprole medocaril	Cephalosporin	G+ve/G–ve
2008	Sitafloxacin	Fluoroquinolone	G+ve/G–ve
2009	Tebipenem pivoxil	Carbapenem	G+ve/G–ve
2009	Telavancin	Glycopeptide	G+ve
2009	Antofloxacin	Fluoroquinolone	G+ve/G–ve
2009	Besifloxacin	Fluoroquinolone	G+ve/G–ve
2010	Ceftaroline fosamil	Cephalosporin	G+ve/G–ve
2011	Fidaxomicin	Tiacumicin*	G+ve
2012	Bedaquiline	Diarylquinoline*	G+ve (TB)

* novel class of antibiotic. G+ve = gram-positive, G-ve = gram-negative, TB = tuberculosis.

Figure 3 Patent applications (families and total) relating to antibiotic research[10]



existing compounds.[12] This trend of divestment is perhaps not surprising given that there are significant scientific, economic and regulatory barriers in the development of antibiotics relative to other medical technologies.[13,14] These barriers are discussed further in the following section.

The situation is not entirely hopeless as there are promising antibiotics currently in development, some of which target the lethal ESKAPE pathogens. Pew Trusts maintains an updated list of current US antibiotics in the clinical stages of development (Appendix 1).[15] While only a US pipeline assessment, it may provide insight into the broader international antibiotic pipeline given that many of the developers are multinational or foreign pharmaceutical companies. As of September 2015, there are an estimated 39 systemic antibiotics in varying clinical phases. Since 2014, the FDA approved six new antibiotics.[16] However, they are within existing classes of antibacterial mechanisms and lack high-priority clinical applicability.

According to additional analysis of Pew's work, 32 of the antibiotics in the pipeline target the "Big 5" indications: complicated urinary tract infection (cUTI), complicated intraabdominal infection (cIAI), acute bacterial skin and skin structure infection (ABSSSI), community acquired bacterial pneumonia (CABP) and hospital acquired pneumonia (HAP) (personal communication, Dr John Rex, Senior Vice President and Chief Strategy Officer of the Infection Business Unit at AstraZeneca, 2016).

Furthermore, 20 of the antibiotics in the US pipeline target gram-negative bacteria, 13 of which target the ESKAPE pathogens. Dr Rex estimated this current pipeline could translate to seven marketable drugs. It should be further noted that six candidate antibiotics solely target C. difficile and only one candidate has an entirely novel mechanism of action, although limited to Pseudomonas.

A position paper by the BEAM Alliance, a consortium of European SMEs developing antibiotics and alternatives, provides a snapshot of the development pipeline of the participating 40 companies (Appendix 2).[17] There is wide variation in the types of therapies in their development pipeline including antibiotics, antibiotic combinations, and alternative therapies such as monoclonal antibodies, bacteriophages and bioproducts. The majority of these products are in Phase I or II, with only one therapy in Phase III.

Alternatives to antibiotics offer promising support to traditional antibacterial agents. Czaplewski et al. recently conducted a portfolio assessment of alternative approaches and found that at least 19 alternative therapies are being explored by academics and industry.[18] Identified alternatives include antibodies, probiotics, lysins, bacteriophages, immune stimulation, vaccines and antimicrobial peptides. However, many of these approaches have yet to be clinically validated and require an estimated £1.5 billion in funding over 10 years in order to be translated into investable ventures and eventually marketable products.

2.3 Barriers within the antibiotic development value chain

In order to target policy that sparks antibiotic innovation, it is important to understand the key scientific, regulatory and economic barriers that underpin the current development pipeline. In late 2015, the German Federal Ministry of Health, in support of the G7's Global Union for Antibiotics Research and Development (GUARD) Initiative, commissioned an advisory consortium to examine the key barriers to antibiotic development.[19] This report uses a useful conceptual framework that identifies the public and private barriers to development across the five major stages of the antibiotic value chain (Figure 4): (1) basic research, (2) preclinical development, (3) clinical development, (4) market approval and (5) commercialization.

Figure 4 Overview of the antibiotic development value chain[19]

Value chain	Basic research	Preclinical development	Clinical development	Market approval	Commercialization
Key activities	• Choosing a target • Screening compound libraries • Discovering and validating hits • Developing lead compounds	• Characterizing the pharmacological profile • Testing toxicity in animal models	• Establishing safety in humans • Determining efficacy in treating infections	• Obtaining approval from drug regulatory authorities	• Producing and distributing the antibiotic • Earning revenue from sales
Challenges	**Discovery Void** Underlying scientific challenges, especially penetration of gram-negative bacteria not resolved	**“Valley of Death”** Many potential leads not taken up in development due to lack of interest and funding – resulting in a brain drain	**Difficult patient recruitment and high cost** Recruiting patients with required pathogens and indications difficult and costs for trials are high	**Insufficient alignment between leading agencies worldwide** Differing standards between regulatory agencies lead to additional costs and effort	**Low market attractiveness** Low and highly unpredictable revenue expectations leading to negative return on investment
Typical duration	4 – 6 years		3 – 5 years	3 – 5 years	3 – 5 years

2.3.1 Barriers to basic research

In the basic research phase of antibiotic development there seems to be what has been termed a 'discovery void'.[19] It appears that big pharmaceutical companies are leaving the critical early stages of drug discovery because basic research tends to be a high-risk phase that will often not result in a marketable drug. A 2006 study examined the success rates of high intensity throughput (HIT) screening for discovery of antibacterial drugs and found that success rates were on average 2.6% from initial HIT screening to reaching Phase I clinical trials.[20] While HIT screening is rarely used now for antibiotic discovery, experts still find that early research success rates are quite low.

High failure rates are in part attributed to the difficulty of applying existing drug discovery strategies to the field of infectious disease, which is constantly morphing. Instead of investing in basic research, large pharmaceutical companies are favouring investment in later stage clinical phases of drug candidates that have been validated by preclinical studies.[1] The divestment of pharmaceutical companies in human and physical resources from basic research activities has lowered the number of dedicated experts in this particular field of antibiotic discovery, a so-called brain drain.[19] The realm of basic research has heavily fallen onto academic institutions, which struggle to find suitable researchers.

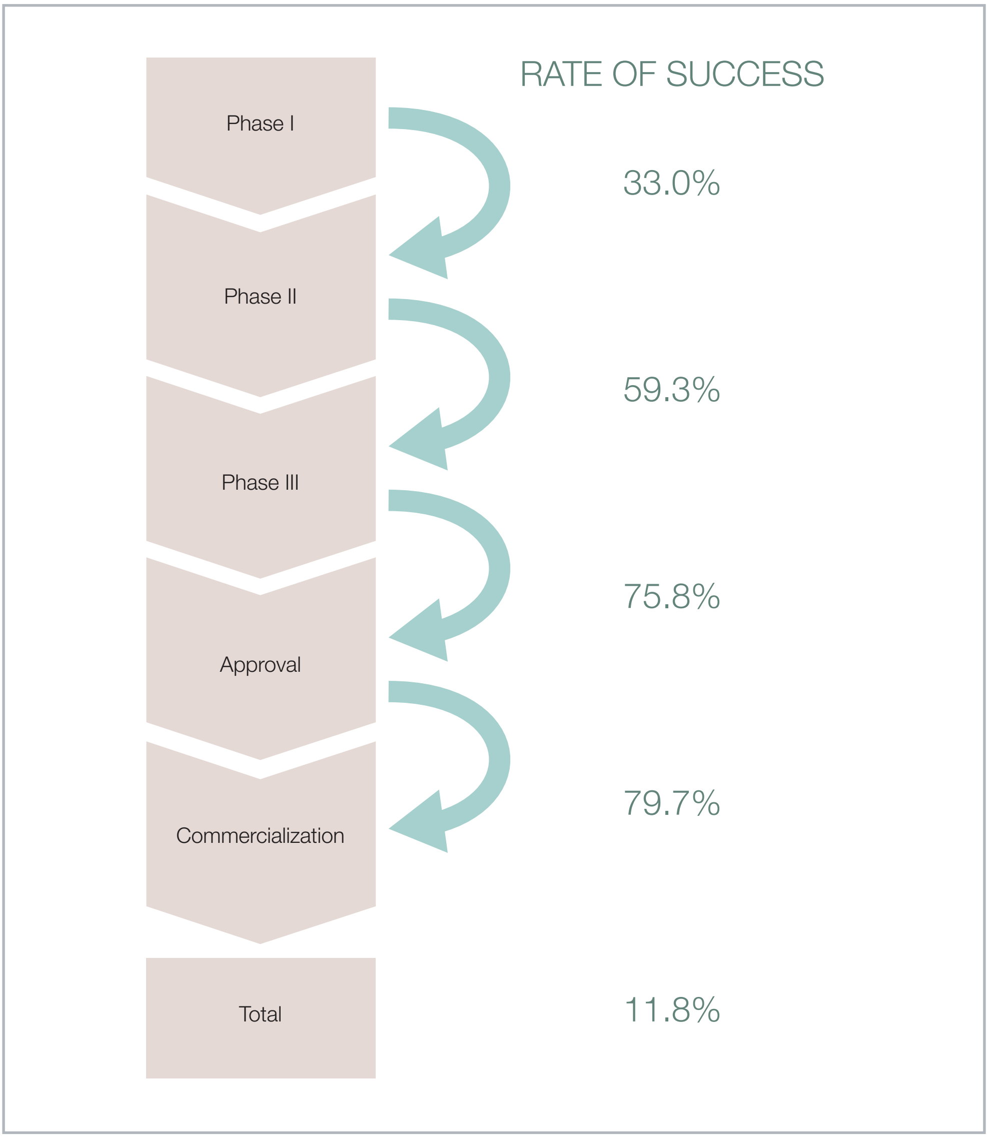
2.3.2 Barriers to preclinical development

The 'valley of death' describes the preclinical phases of transitioning a lead compound to a drug candidate ready for human testing.[19] It straddles basic research and clinical development where there are often weak translational links between academia, non-profits and industry. Preclinical development is considerably more expensive than basic research and thus many academic and non-profit institutions are unable to afford moving their lead compound to further development. Meanwhile, pharmaceutical companies determine preclinical development based almost solely on commercial viability. As a result, there is an inefficient silo effect created among key antibiotic players often resulting in a duplication of efforts in the preclinical realm.[21]

2.3.3 Barriers to clinical development

Once an antibiotic has reached the clinical phases, success rates for marketability significantly increase (Figure 5) and are actually relatively higher compared to other drugs.[19,22] However, there is still a high cost required to properly test an antibiotic product through the three phases of randomized controlled trials (RCTs). The UK AMR Review estimates that the clinical development cost for one marketable antibiotic costs €120 million.[5] However, this figure does not include the cost of the many failed candidates. The Review further estimates the true cost of developing one antibiotic, from basic research to commercialization, is approximately €700 million to €1.1 billion. A significant portion of this substantial cost is from clinical development.

Figure 5 Success rate of antibiotic development from Phase I to market[19]



These development costs are prohibitively high for many SMEs, which may not have the available capital to invest in promising candidates.[1,17] Despite this disadvantage, small pharmaceutical firms and biotechnology companies are the primary investors in antibiotic development. In 2014 the top 25 pharmaceutical companies maintained only 15% of the share of antibiotics in clinical development.[5] In stark contrast, the top 25 pharmaceutical companies spend 67% of the global pharmaceutical R&D budget.[23]

Lastly, the combination of few rapid point-of-care diagnostic tools and short treatment times for acute bacterial infections makes recruiting patients logistically challenging. Until only recently, there has been no centralized database to identify patients suitable for participation in an antibiotic RCT. However, as part of the Innovative Medicines Initiative's (IMI) project COMBACTE, a clinical trials network for antibiotic development has been established across Europe (discussed in more detail below). Moreover, there is an undersupply of expert practitioners in a particular bacterial disease field that can adequately lead an RCT.

2.3.4 Barriers to market approval

The EMA and The US Food and Drug Administration (FDA) recognize that there is regulatory uncertainty and differences between the two market authorization processes for antibiotics.[6] These differences pertain to patient selection criteria, definition of clinical endpoints, specification of statistical parameters and rules regarding expedited approvals.[19] Consequently, ensuring that a drug meets the clinical requirements for both regulatory agencies can be costly. Greater harmonization between the EMA and FDA is a key goal of TATFAR.[6] Complicating matters further, the differences in licensing requirements between the EMA and FDA are relatively minor in comparison to the licensing practices of other drug regulatory authorities such as the China Food and Drug Administration and Japan's Pharmaceuticals and Medical Devices Agency.

2.3.5 Barriers to commercialization

An Office of Health Economics (OHE) report calculated that the average net present value (NPV) for an antibiotic project is -$50 million USD.[22] The estimated NPVs for musculoskeletal drugs and neurological drugs are +$1.15 billion and +$720 million respectively.[22] The low NPV for antibiotics particularly stems from low revenue potential after it has been marketed. This arises because antibiotic sales volumes and prices are low.[19] Expected sales volumes for new antibiotics are low because there is an established set of competitors in the market, antibiotics are typically used for only short durations, and stewardship programmes encourage restricted use of antibiotics. Sales are further threatened by development of new diagnostic tests that could decrease the inappropriate use of antibiotics.[24] Prices of antibiotics tend to be low despite their high value in health care because of intense market competition.[19] Many antibiotic treatments can cost less than €40 for a week-long treatment course in contrast to cancer therapies which can reach prices of over €90,000 for a yearlong treatment.

As a result, many experts consider the antibiotics business model to be broken. Multiple new models have been suggested such as the Antibiotic Conservation Effectiveness (ACE) programme, the Options Market for Antibiotics (OMA), the Antibiotic Health Impact Fund (AHIF) and the Antibiotic Innovation Funding Mechanism (AIFM).[25–28] Many new antibiotic business models build on the concept of 'delinkage', the separation of revenues from sales volume in order to ensure that developers are not pushing sales and increasing the potential for further resistance development.[24]

2.4 Incentives to spark innovation in the antibiotics market

Research and development of neglected drugs, such as antibiotics, can be incentivized through two broad strategies known as push and pull mechanisms (Table 2).[1,29] Push methods reduce the cost of researching and developing new drugs. This is accomplished through increasing access to scientific resources, providing research grants, offering tax incentives and establishing partnerships for dividing R&D costs. In contrast, pull mechanisms reward successful development of a drug by increasing or ensuring future revenue. Pull mechanisms can be outcome based as seen with monetary prizes, advanced market commitments (AMCs) and patent buyouts. Alternatively, they may invoke lego-regulatory policies such as accelerated drug assessment pathways, market exclusivity extensions, anti-trust reforms and value-based reimbursement. These push and pull strategies understandably have distinct advantages and disadvantages, as well as target different barriers in the antibiotic value chain. Experts tend to agree that a combination of complimentary incentives will be needed to effectively stimulate R&D in antibiotics.

Table 2 Basic push and pull incentives for encouraging and fostering antibiotic R&D[30]

Push incentive strategies	
• Supporting open access to research	• Funding translational research
• Grants for scientific personnel	• Tax incentives
• Direct funding	• Refundable tax credits
• Conditional grants	• Product development partnership
Outcome-based pull incentive strategies	
• End prize	• Research tournament
• Milestone prize	• Advanced market commitment
• Pay-for-performance payments	• Strategic Antibiotic Reserve
• Patent buyout	• Service-availability premium
• Payer license	
Lego-regulatory pull incentive strategies	
• Accelerated assessment and approval	• Anti-trust waivers
• Market exclusivity extensions	• Sui generis rights
• Transferable intellectual property rights	• Value-based reimbursement
• Conservation-based market exclusivity	• Targeted approval specifications
• Liability protection	• Priority review vouchers

In late 2014, the UK Economic and Social Research Council, on behalf of Jim O'Neill's AMR Review, commissioned Renwick, Brogan and Mossialos to conduct a systematic review of existing push and pull incentive strategies for encouraging development of novel antibiotics.[30] This review identified 47 different strategies, ranging from single push or pull incentives to complex proposals combining multiple incentives that restructure the entire antibiotic business model. Furthermore, this paper puts forward a framework that can be used by policy makers to design a comprehensive incentive package that encourages and fosters development of novel antibiotics.

The framework can be broken down into three successive steps. The first step involves choosing a core incentive package that addresses key economic criteria necessary for re-balancing the market. This core incentive package must: improve the NPV of antibiotic project development; make antibiotic development possible for SMEs; encourage participation of large firms; and foster synergy among all stakeholders in the market. The second step requires the core market incentive package to be amended to attain public health goals pertaining to antibiotic stewardship and patient access to necessary antibiotics. The last step considers the package's implementation and operational feasibility, which is distinct to national context.

2.5 Funding landscape for the development of antibiotics

The funding landscape can be looked at from the perspective of both public and private investments. A comprehensive study by Kelly et al. published in 2016 in *The Lancet Infectious Diseases* assessed public funding for antibacterial resistance research* in 19 JPIAMR countries, the EC and related EU agencies between 2007 and 2013.[31] Data from this study highlights that total public investment in 1,243 projects was €1.3 billion for this time period (Table 3).

Funding was assessed across six priority areas in antibacterial resistance related research: therapeutics, diagnostics, surveillance, transmission, environment and interventions. In the present report, we are concerned with the categories of therapeutics, which includes antibiotic and alternative therapy R&D, and diagnostics (Table 4). In total €626 million was invested between 2007 and 2013 at national and European levels (excluding the IMI) in antibacterial therapeutics and €129 million was invested in diagnostic tools. The IMI is composed of nine projects and makes up a significant portion of total antibacterial funding and is primarily dedicated to therapeutics.

Therapeutics can be sub-categorized as follows: underpinning research in antibacterials, (II) research in alternative therapies, (III) research in optimizing existing therapies, (IV) lead-to-trial pre-clinical and clinical development and (V) multiple components (i.e.

* Antibacterial resistance research is a subset of AMR research. Thus, the funding figures for antibacterial resistance research shown in Kelly et al.'s study represent a portion of the total funding for AMR research by JPIAMR countries and the EU.

Table 3 Total committed public funding to antibacterial resistance research by JPIAMR countries and the EU, 2007–13[31]

	Total number of projects, 2007–13	Total funding (€), 2007–13	Proportion of total funding (excluding EC contributions to IMI)	Proportion of total funding
19 JPIAMR countries	1129	646,646,541	67.3%	49.5%
EU level[a]	114	659,201,418	NA	50.5%
EU level (excluding IMI)	105	314,128,438	32.7%	24.1%
IMI (EC contribution only)	9	345,128,438	NA	26.4%
Overall	1243	1,305,847,959	100%	100%

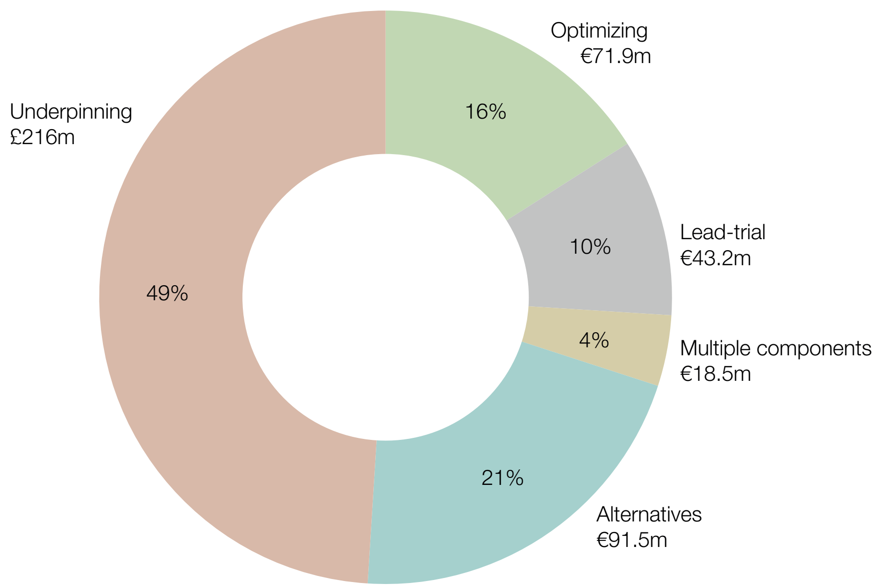
[a] EU level = EU level (excluding IMI) + IMI (EC contribution only).

Table 4 Total committed public funding from 2007–13 to therapeutic and diagnostic antibacterial research by JPIAMR countries and the EU[31]

	19 JPIAMR Countries		EU Level (excluding IMI)		Total	
	No. projects	Funding (€)	No. projects	Funding (€)	No. projects	Funding (€)
Therapeutics	763	428,199,158	71	197,432,615	834	625,631,773
Diagnostics	131	90,353,417	13	38,266,222	144	128,619,639

projects focusing on more than one of the above sub-categories). Figure 6 highlights the breakdown of national level funding across these therapeutic subcategories. Notably, only 10% of national level funding was dedicated to drug development preclinical and clinical trials and only 4% was dedicated to multi-component research projects that may include preclinical and clinical studies. This is likely due to the existing strength of basic bacteriology and resistance research across many JPIAMR countries. In addition, public institutions have traditionally tended to not directly fund clinical trials led by pharmaceutical companies, however this trend is beginning to change (personal communication, Ruth Kelly, Antimicrobial Resistance Science Programme Manager, UK MRC, 2016).

Figure 6 European national-level funding of therapeutic-related antibacterial resistance projects by therapeutic sub-category (2007–13)[32]



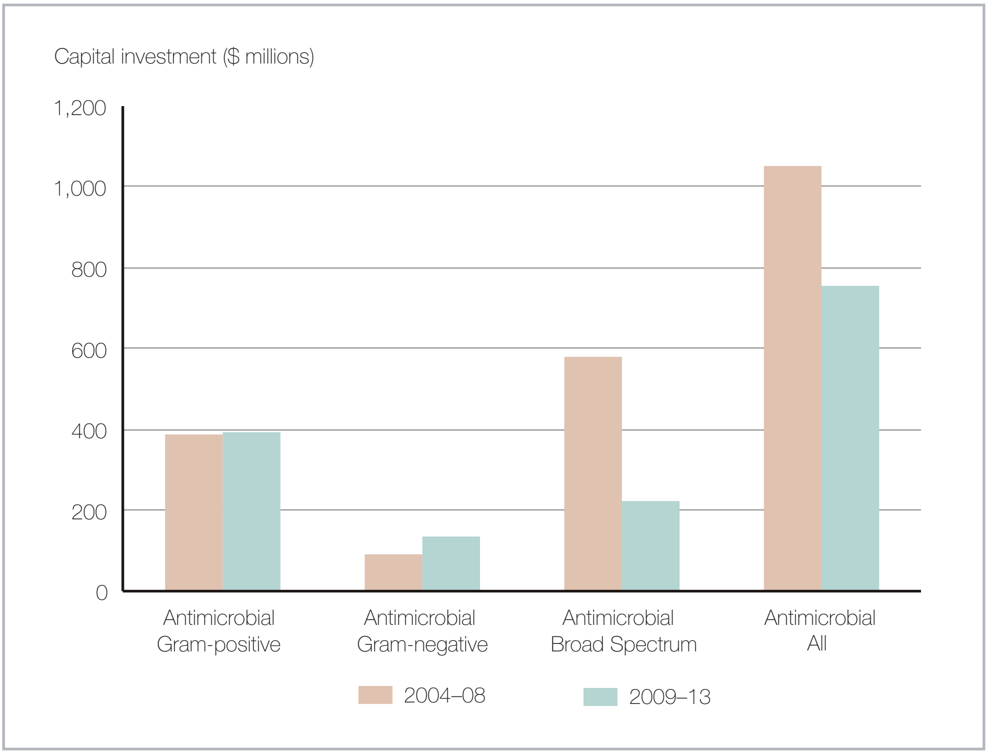
Providing a picture of private sector funding for antibiotics, the Biotechnology Industry Organization (BIO) conducted an analysis of four major venture capital databases over the ten-year period, 2004 to 2013.[33] These databases capture $38 billion in venture capital invested in over 1,200 drug companies across the world. According to this BIO report, approximately $1.8 billion in venture capital was invested in the R&D of antimicrobials between 2003 and 2013 (Table 5). Venture capital investment in all antimicrobials declined by 28% across the two five-year windows in this timeframe. The report further noted that venture capital appears to have increased by 51% in the field of gram-negative antimicrobial R&D, yet still only captures 12% of total investment (Figure 7). In contrast, the field of broad-spectrum antimicrobial R&D declined by 61%. Gram-positive antimicrobial R&D remained steady.

It is important to appreciate that this venture capital data does not provide insight into how much of their internal capital individual firms are investing in antibiotic R&D. Additionally, this data does not indicate what types of companies were being funded (i.e. big pharmaceutical companies vs. SMEs) through external private financing.

Table 5 Global venture capital investment in antimicrobial R&D between 2004 and 2013[33]

	2004–08 ($ millions)	2009–13 ($ millions)	2004–13 ($ millions)	Change 2004–08 to 2009–13
Antimicrobial Gram-positive	386	394	780	+2%
Antimicrobial Gram-negative	89	134	223	+51%
Antimicrobial Broad Spectrum	578	225	803	-61%
Antimicrobial All	1,053	753	1,806	-28%

Figure 7 Venture capital investment for antimicrobial R&D, 2004–08 vs. 2009–13[33]



3. Research Methodology

Our research methodology can be divided into three phases. The first phase involved collecting information and evidence on the existing set of initiatives that support R&D of human antibiotics, alternative therapies and diagnostic devices*. This step involved a semi-systematic literature review supplemented by input from experts in the field**. Using this evidence, we constructed case studies for the major antibiotic R&D initiatives. The second phase entailed performing an in-depth analysis of each initiative using evaluation criteria identified from the literature. This analysis supplemented the case studies and provided a basis for policy discussion of antibiotic R&D. The final phase consisted of consolidating a concise set of recommendations that arose from our analysis and policy discussion. For the purposes of this report, the term “initiative” refers to both programmes and institutions that target innovation in antibiotic drug discovery and development.

3.1 Literature review

Through a semi-systematic literature search we identified current and proposed policy initiatives that foster R&D of novel antibiotics, alternative therapies and diagnostic devices. We reviewed relevant peer-reviewed articles with use of MEDLINE (PubMed), Embase (Ovid) and Web of Science. Search terms included: “antibiotic”, “antimicrobial”, “antibacterial”, “resistance”, “resistant”, “alternative”, “diagnostic”, “devices”, “research”, “development”, “incentive”, “policy”, “mechanism”, “business model”, “strategy”, “instrument”. The search was restricted to papers published in the last five years, in English, and either comments, editorials, journal articles, reviews, or systematic reviews. Additional non-peer reviewed literature was included in this report and identified through a Google search, and from citations in several key papers and publication archives on relevant websites.

3.2 Expert input

Once an initial compilation of initiatives had been established, we solicited expert input to ensure that we had correct information and had not missed pertinent initiatives (Figure 8). In collaboration with the Dutch Ministry of Health, Welfare and Sport, we selected experts that were associated with the major initiatives identified in our literature review.

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* We limited the scope of our research to only antibiotic products for humans, however we recognize that R&D of veterinary antibiotics is an important aspect of the One Health approach to AMR.

** A semi-systematic literature review or rapid literature review follows a predetermined structured format for compiling and identifying relevant information from peer-reviewed and non-peer-reviewed sources. However, it does not include the same degree of review repetition that would be associated with a complete systematic literature review. Due to time constraints, a semi-systemic review structure supplemented by extensive peer consulting was used instead of a systematic review structure.

Figure 8 List of organizations that provided expert input on the compilation and basic assessment of identified antibiotic R&D initiatives

- Antibiotic Research UK
- Antimicrobial Resistance and Health Acquired Infections Program, European Centres for Disease Control and Prevention
- Astellas
- AstraZeneca
- BEAM Alliance
- Broad Spectrum Antimicrobials Program, Biomedical Advanced Research and Development Authority, US Department of Health and Human Services
- Canadian National Research Council
- European Federation of Pharmaceutical Industries and Associations
- European Medicines Agency
- GlaxoSmithKline
- Innovative Medicines Initiative
- Institute of Infection and Immunity, Canadian Institutes of Health Research
- Joint Programming Initiative on Antimicrobial Resistance
- Directorate General for Research and Innovation, European Commission
- Merck
- Ministry of Health, Welfare and Sport, Dutch Government
- National Institute of Allergy and Infectious Diseases, US National Institutes of Health
- Office of Antimicrobial Resistance, US Centers for Disease Control and Prevention
- Office of Life Sciences, UK Government
- Organisation for Economic Co-operation and Development
- Pew Charitable Trusts
- Public Health Agency of Canada
- The UK Review on Antimicrobial Resistance
- Swedish Research Council
- UK Medical Research Council
- Vinnova
- World Health Organization

Experts related to an initiative provided feedback regarding their initiative's priorities, operational programmes, R&D incentive mechanisms and funding. Further phone interviews were conducted with select experts to learn more about particular major initiatives. The analyses and discussion of this report are based on the authors' assessment and do not necessarily reflect the opinions of the experts consulted in the process.

3.3 Country case studies

Using a combination of our primary and secondary research, we drafted short case studies of the major antibiotic R&D initiatives at international, EU and national levels. These case studies provide an overview of the various initiatives and each one is complimented by a brief analysis based on the framework discussed in the following section.

3.4 Framework for initiative analysis and discussion

Initiatives were analysed based on their underlying incentives used to facilitate discovery and development of antibiotics and related medical products (Table 6). Some initiatives provide only indirect support for antibiotic R&D by coordinating strategic actions on AMR. While these strategic initiatives are important to effectively stem antibiotic resistance, this report generally focuses on the initiatives that provide direct antibiotic R&D incentives.

In the first phase of our initiative assessment, we identified:

1. The type of incentives used (i.e. push vs. pull)
2. The antibiotic value chain barriers targeted by these initiatives (i.e. basic research, preclinical development, clinical development, market approval and commercialization)
3. The amount of funding backing the initiatives

Subsequently, we further analysed the initiatives that employed direct incentives. This secondary analysis looks at the critical actions required of a comprehensive and effective incentive package as proposed by Renwick et al.[30] Therefore, we examined whether a particular initiative as a whole fulfilled the following:

1. Improved antibiotic R&D NPV
2. Supported SMEs throughout the antibiotic value chain
3. Enticed large pharmaceutical companies to participate in the antibiotics market
4. Encouraged stakeholder synergies
5. Promoted antibiotic stewardship and patient access
6. Addressed specific high-priority medical needs (e.g. antibiotics targeting Gram-negative bacteria)

Based on our evidence collection and analysis, we compiled a set of key policy questions that deserved further discussion. This discussion ultimately informed our final recommendations, in Section 6, regarding further enhancing global and European antibiotic R&D.

Table 6 Outline of analysis framework applied to antibiotic R&D initiatives

First-tier assessment	• What types of push and pull incentives are used under this initiative? • Which barriers are targeted in the antibiotic value chain by this initiative? • How much funding is available to this initiative?
Second-tier assessment	• Does this initiative improve antibiotic project NPV? • Does this initiative enable SMEs to participate in antibiotic R&D? • Does this initiative engage large-cap pharmaceutical companies to participate in antibiotic R&D? • Does this initiative facilitate any form of collaboration and synergy among relevant stakeholders? • Does this initiative promote the goals of antibiotic conservation and patient access? • Does this initiative target specific high-priority medical need?

Our initiative analyses, discussion and recommendations are founded on our own views and do not explicitly reflect the opinions of the numerous experts that provided input on this report.

4. Results

The following results section explores the most impactful initiatives identified at international, EU and national levels. We first provide an overview of each initiative's agenda and programmes. Then we provide a brief analysis of each initiative according to the framework discussed above. A comprehensive summary table of all the initiatives identified in our research can be found in Appendix 3. Appendix 4 provides a criteria-based assessment of the initiatives that provide direct incentives for antibiotic R&D. The Appendix 4 assessment focuses just on the initiatives with direct incentives because initiatives that coordinate activities and strategies (e.g. TATFAR, DRIVE-AB, Global Action Plan, etc.) generally aim to achieve all the criteria.

4.1 Key international initiatives that foster R&D of antibiotics

■ Joint Programming Initiative on Antimicrobial Resistance

Overview: The Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) is an international collaboration effort focused on streamlining and coordinating research in the field of AMR.[34] Established in 2011, the JPIAMR is now comprised of 22 member countries including numerous EU states, Switzerland, Canada, Israel, Turkey, Argentina and Japan. The JPIAMR directs national funding from these countries towards research projects that fill key knowledge gaps in AMR and aligns their national research efforts. In addition, the JPIAMR aims to support research through establishing a database compiling veterinary and human AMR research, collaborating with key stakeholders and raising public awareness of AMR. Their strategic research agenda outlines six key areas of future investment in AMR research priorities: therapeutics, diagnostics, surveillance, transmission, environment and interventions.

The JPIAMR's first joint call for transnational research was published in early 2014 and the research projects started in early 2015. This €8.1 million first call, known as "InnovaResistance: Innovative approaches to address antibacterial resistance", is composed of 7 research projects that address key issues such as infection, treatment development, target identification for antibacterial drug development and pharmacokinetics. The second JPIAMR joint call will be exploring ways to minimize the incidence of AMR through reviving neglected and disused antibiotics (ND-AB), designing innovative combinations of ND-AB and antibiotics, and creating combinations of ND-AB and non-antibiotics. This project has funding of €4.5 million. Closed recently, the JPIAMR's third research call is a €30 million joint project with the EC that will foster multinational research collaborations to improve the control of human and veterinary bacterial infections. Lastly, the fourth joint call will solicit leading scientists to establish global research networks for the development of guidelines and best practice frameworks in AMR. The fourth joint call opened in April 2016 and closes in June 2016.

Analysis: The JPIAMR provides antibiotic R&D incentivization in the form of direct research funding (push) and by providing an international forum for collaboration between researchers (push). The targeted value chain barrier of this initiative is basic and preclinical research and thus academic groups are the primary benefactors. In fact, all the research partners listed for the first joint research call were universities or non-profit research organizations such as the Pasteur Institut. An international forum for AMR research collaboration such as the JPIAMR has the potential to disseminate novel research, minimize duplications in research, assemble expertise in AMR and pool funding resources from its national partners. In addition, the JPIAMR is helping to identify key research priorities in AMR and then to allocate research responsibilities to various academic institutions. The early stage focus on basic research means that these incentives do not particularly reinforce stewardship programmes or patient access to developed antibiotics down the line.

■ Transatlantic Task Force on Antimicrobial Resistance

Overview: Created in 2009, The Transatlantic Task Force on Antimicrobial Resistance (TATFAR) is a cooperative agreement between the EU and US to harmonize government strategies combating AMR.[35] Members of TATFAR include the key health regulatory, funding, and administrative bodies from the EU and US (Figure 9). The TATFAR has 15 ongoing recommendations across three priority areas: "(1) appropriate therapeutic use of antimicrobial drugs in medical and veterinary communities, (2) prevention of healthcare and community-associated drug-resistance infections and (3) strategies for improving the pipeline of new antimicrobial drugs."[35] Of particular relevance to this report are the recommendations made regarding development of new antibiotic drugs. Broadly they call for greater financial incentives for private firms, improved communication between

Figure 9 Member organizations of TATFAR[6]

US Member Organizations	• Department of Health and Human Services • Centers for Disease Control and Prevention • Food and Drug Administration • National Institute for Allergy and Infectious Disease, National Institutes of Health
EU Member Organizations	• Directorate General for Health and Consumers, European Commission • Directorate General for Research and Innovation, European Commission • European Centre for Disease Prevention and Control • European Medicines Agency • European Food Safety Authority • Council of the European Union

US and EU drug regulatory and research bodies, increased basic research funding, harmonized regulatory pathways for antibiotics and open sharing of information on drug development. It is the responsibility of the relevant member organizations to implement these recommendations.

Analysis: TATFAR does not provide any direct incentives for the R&D of antibiotics given that its' mandate is to facilitate inter-organization and international communication, discussion and harmonization. However, TATFAR brings together the critical government agencies involved in making decisions on antibiotic R&D funding, drug approval requirements, and market policies and regulations. TATFAR has the potential to implement incentives indirectly through it member organizations.

■ European and Developing Countries Clinical Trials Partnership

Overview: Formed in 2003, the European and Developing Countries Clinical Trials Partnership (EDCTP) is an evolving public-private partnership (PPP) between 14 European countries and 14 African countries to accelerate the clinical development of drugs for poverty-related neglected infectious diseases.[36] The EDCTP supports research collaboration between clinical researchers from academia, public health institutes, pharmaceutical companies, PDPs and relevant non-governmental organizations (NGOs). Human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS), tuberculosis (TB), malaria and neglected infectious diseases that are endemic to sub-Saharan Africa are the primary focus of the EDCTP programme.

Drug resistance is a major issue in treating many of these diseases and thus is included as an important challenge in the EDCTP's strategic agenda. The first EDCTP programme, spanning 2003 to 2013, had funding of approximately €1 billion, of which around €200 million was sponsored through the EC's Sixth Framework Programme (FP6). The second EDCTP programme (EDCTP2) is currently being implemented as another 10-year programme (2014–2024). The EC is providing a contribution of up to €683 million with the expectation that member states will match contributions. The total funding for the new programme, including expected contributions from other countries, the private sector, NGOs and other third parties, is estimated to be €2 billion (personal communication, Dr Adrianus van Hengel, Scientific Officer, DG Research and Innovation, European Commission, 2016).[36]

EDCTP's funding is concentrated on R&D for treatment drugs, vaccines, alternative therapies like microbicides and diagnostic tools that target HIV/AIDS, TB, malaria and other poverty-related infectious diseases, including those that are susceptible to AMR. EDCTP2 supports all stages of clinical development (I to III), including Phase IV post-marketing studies.[36] In addition, EDCTP supports networking and capacity building in sub-Saharan Africa to ensure a conducive environment and reliable capacity to conduct clinical research and trials according to established international standards and in compliance with European, national, or regional legislation. Consequently, the EDCTP initiated and supported the establishment of four African Regional Networks of Excellence for

Table 7 EDCTP's drug R&D project portfolio, 2003–14[36]

Target disease	Number of drug R&D projects	Funding for drug R&D projects (€ million)
HIV/AIDS	20	25.08
TB	10	30.10
Malaria	22	30.13
HIV/TB co-infection	8	7.23

clinical trials tasked to collaborate and coordinate clinical trials and treatment development. Finally, the EDCTP provides individual fellowships to promote training and career development of researchers, clinicians and regulatory experts in sub-Saharan Africa.[36]

Analysis: The EDCTP forms one of the four key pillars of the EC's strategy to fight AMR – the other three being the framework programmes for research (FP6, FP7 and Horizon 2020), the JPIAMR and the IMI programme. The EDCTP has been successful in fostering R&D of antibiotics and related products as evidenced by the programme's extensive drug development portfolio, which includes multiple Phase III clinical trials (Table 7).[36] It provides direct funding of the R&D resources and infrastructure required to move a drug candidate through the clinical development phase. In addition, EDCTP engages sub-Saharan African countries in the R&D process as well as the private sector. However, it does appear that EDCTP's industry partnership is heavily weighted towards the big pharmaceutical companies such as GSK, Sanofi and Merck. It is unclear how, or if at all, the EDCTP pulls potential novel antibiotics through the market approval stages and eventual commercialization process. The EDCTP's ultimate goal of improving access to effective treatments for poverty-related and neglected infectious diseases aligns well with current public health priorities. However, patient access and antibiotic stewardship are difficult to balance, particularly in developing countries where appropriate use of antibiotics is difficult to control. Thus, it is unclear how the EDCTP aims to facilitate appropriate use of any novel antibiotics that are produced through the initiative.

■ Global Action Plan on Antimicrobial Resistance

Overview: The Global Action Plan on AMR was endorsed at the 68th World Health Assembly in May 2015.[37] It is a global call to action among all member states, the United Nations (UN) Secretariat, the WHO, international organizations and other relevant partners. The overriding goal is to "treat and prevent infectious diseases with effective and safe medicines."[37] It focuses on using a One Health approach as well as promoting access to medicines for those in need across countries of all income levels. In order to achieve this broader goal, one of its strategic objectives is to make an economic case for sustainable investment in new antibiotics, diagnostic tests, vaccines and other interventions.

The Global Action Plan called for the creation of a new partnership, called the Global Antibiotic R&D Facility, to foster the development and conservation of antibiotics.[38] The WHO and the Drugs for Neglected Diseases Initiative (DNDi) are working in collaboration on this partnership to develop novel antibiotics, as well as promoting their responsible use and ensuring equitable access. This partnership model is based on previous experience with neglected diseases and will specifically focus on global public health needs. Thus, the WHO/DNDi initiative will focus on R&D gaps in which neither industry nor academics are currently engaging. In doing so, it will encourage close collaboration with the public and private sectors, including government agencies, NGOs, pharmaceutical companies and academia. Three million euros in seed funding is required for the initial two-year start-up phase.

Analysis: The Global Action Plan is designed to encourage the development of novel antibiotics using an integrative and cooperative approach. It is a strategic plan that coordinates worldwide AMR action, thus itself does not offer direct antibiotic R&D incentives. But, the Global Antibiotic R&D Facility aims to implement part of this plan.

While this facility is still in the planning phases it aims to target all levels of the antibiotic value chain from the basic research level to the commercialization phase. DNDi has successfully developed a pipeline of drugs and treatments for multiple neglected diseases and thus is a valuable collaborator to work with in the fight against AMR. Possible incentives include the use of milestone prizes, which will act as push and pull incentives to encourage antibiotic development. In addition, the strong emphasis on collaboration with all stakeholders encourages synergy across the antibiotic market. It may play a complementary role to other initiatives such as the JPIAMR, BARDA and IMI, which will encourage further synergy across the global antibiotics market.

■ G7 Global Union for Antibiotics Research and Development Initiative

Overview: The Global Union for Antibiotics Research and Development (GUARD) arose from the 2015 Berlin Conference of G7 Health Ministries.[19] GUARD is an agreement among G7 nations that a collaborative approach among countries is required to effectively fight AMR. It is recognized that continued efforts are needed to stimulate the antibiotic R&D pipeline.

This initiative proposes priority areas for action and recommendations to stimulate antibiotic R&D. It explores how economic incentives can contribute to antibiotic R&D and it targets incentives along all areas of the antibiotic value chain, recommending levers at each stage.[19]

Analysis: GUARD recognizes that individual countries have created incentives to encourage R&D but also recognizes that a global response is necessary to fully effect change. An international approach is required to encourage engagement of the pharmaceutical industry with antibiotic development and to coordinate research to avoid duplication. This initiative recommends a global antibiotic collaboration platform to foster R&D. While this initiative has important implications in global coordination of antibiotic R&D action, as of now, there are no concrete incentives that back its calls to action.

4.2 Key EU initiatives that foster R&D of antibiotics

■ Directorate-General for Research and Innovation, European Commission

Overview: The EC's Directorate-General for Research and Innovation (DG RTD) funds numerous R&D projects related to AMR. These projects range in size from single research endeavours to multifaceted and coordinated programmes. The DG RTD's funding for AMR projects comes from FP6, Seventh Framework Programme (FP7) and Eighth Framework Programme, known as Horizon 2020. Altogether, the FP7 has provided €1.08 billion in EC funding for 147 AMR projects. Starting in 2014, Horizon 2020 has funded 145 AMR projects so far with a budget of €316 million* (personal communication, Dr Adrianus van Hengel, Scientific Officer, DG Research and Innovation, European Commission, 2016).

The IMI and EDCTP are two of the largest drug R&D programmes operating under the partial governance of the DG RTD and funded with FP6 and FP7. Both these programmes have dedicated significant resources to R&D of antibiotic products. The DG RTD is now beginning to roll out the second iterations of the IMI (IMI2) and EDCTP (EDCTP2), funded through Horizon 2020.

The DG RTD funds numerous individual projects related to antibiotic development separate from the IMI and EDCTP. Notably, many of these individual projects target innovation in SMEs. The DG RTD offers SME-focused financing opportunities through programmes such as the SME Instrument, the Fast Track to Innovation pilot scheme and the Eurostars programme. These are general funding programmes for innovation that are not restricted to AMR research, but nonetheless are accessible to SMEs pursuing antibiotic R&D. Funded within FP7, 7 SME research projects on novel antibiotics, vaccines and alternative medicines were launched in 2013, with budgets of over €90 million. As of 2014, Horizon 2020 is funding 28 AMR projects through the new Horizon 2020 SME Instrument, which will fund SME antibiotic R&D. Of additional interest is the Horizon 2020 Better Use of Antibiotics Prize, which is a €1 million prize for developing a rapid point-of-care test to identify patients with upper respiratory tract infections that can be treated without antibiotics.[39]

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* The EC contribution to IMI is not included in the budget figures presented for the FP7 and Horizon 2020.

Analysis: The DG RTD is one of the largest funding bodies supporting R&D in antibiotics, alternative medicines and diagnostic tools. The DG RTD is able to bring together many of the key stakeholders throughout the antibiotic value chain and allocate significant resources pooled from the EU's budget. Of particular value are the DG RTD's numerous funding opportunities for SME ventures in antibiotic R&D. However, the breadth in scope and large size of some of these programmes makes it difficult to accurately assess the effectiveness of the DG RTD in terms of antibiotic R&D. The diagnostics prize (pull) is an interesting departure from the R&D push funding typically offered by the DG RTD. Alas, the €1 million reward is a relatively small denomination.

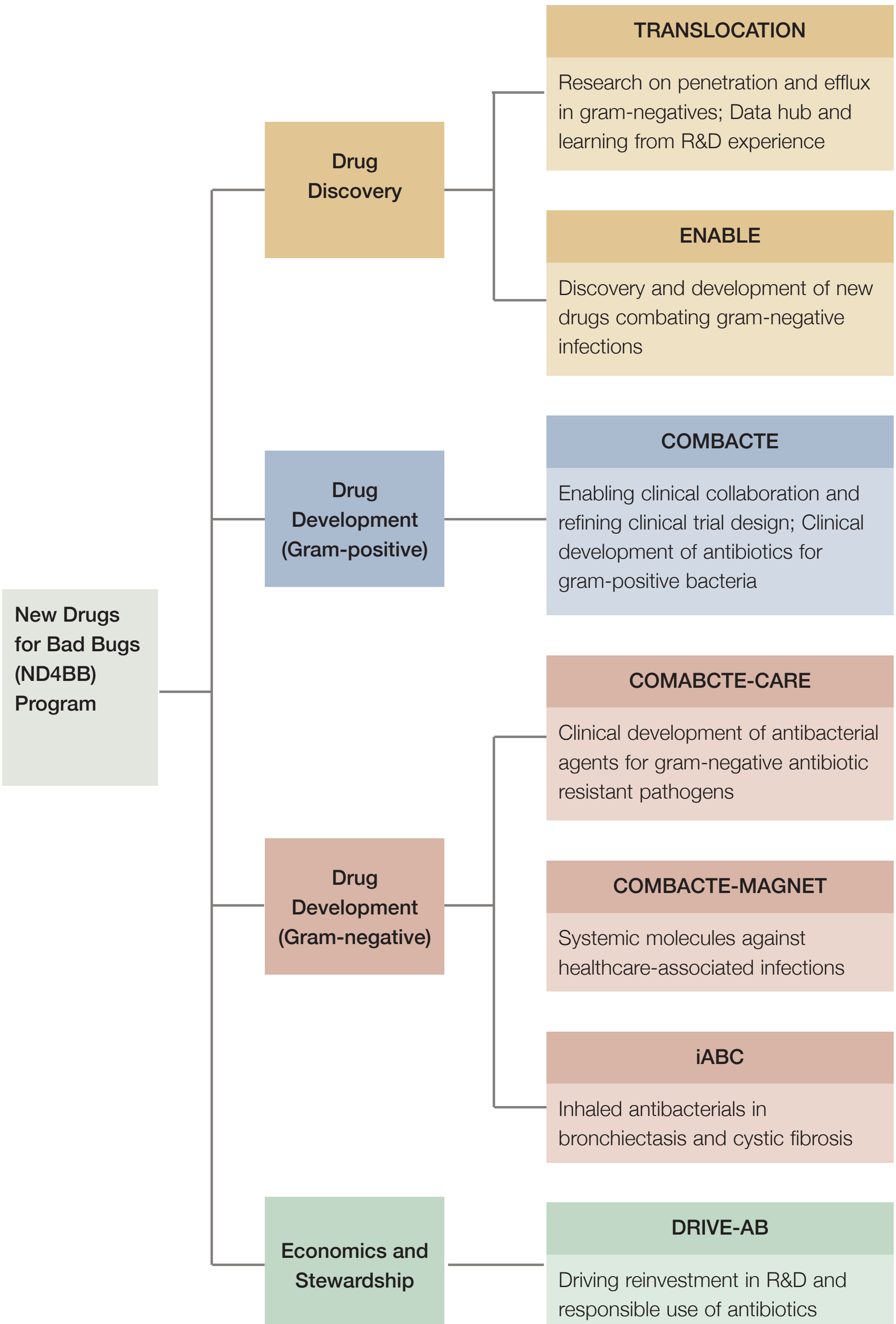
■ New Drugs for Bad Bugs, Innovative Medicines Initiative

Overview: Launched in 2008, the IMI is a public-private partnership between the EU and the European Federation of Pharmaceutical Industries and Associations (EFPIA).[40] The IMI brings together key stakeholders involved in healthcare R&D: universities, pharmaceutical companies, SMEs, patient organizations, medicines regulators and health research companies. The IMI has a total budget of over €5 billion funded equally by the EC (under the FP7 and now Horizon 2020) and by in-kind contributions from the EFPIA. The initiative currently has over 70 projects that tackle various areas of unmet medical and social need such as Alzheimer's disease, schizophrenia, depression, chronic pain, autism and AMR. Beneficiaries of the IMI are selected through a competitive call and evaluation process with the help of independent experts (personal communication, Dr Adrianus van Hengel, Scientific Officer, DG Research and Innovation, European Commission, 2016).

Established in 2012, The New Drugs for Bad Bugs (ND4BB) programme is an IMI partnership, tasked with improving the discovery and development of novel antibiotics.[41] There are seven core ND4BB projects with a total committed budget of €606 million, of which €317 million is contributed by the EC's FP7.[42] These seven projects have been tailored to target different R&D barriers to the marketing of novel antibiotics (Figure 10). The projects TRANSLOCATION and ENABLE are focused on assisting early stage antimicrobial drug discovery; COMBACTE facilitates drug development of antibiotics targeting gram-positive bacteria; COMBACTE-CARE, COMBACTE-MAGNET and iABC aim to tackle the drug development barriers of antibiotics targeting gram-negative bacteria; and finally DRIVE-AB looks at the economic and stewardship aspects of AMR. In addition to these core seven ND4BB programmes, the IMI also has the RAPP-ID programme, developing a rapid point-of-care test for infectious diseases and the PreDiCT-TB programme, optimising the use of preclinical information for the development of drugs that target resistant TB.[41]

The largest project within ND4BB is COMBACTE, which has built four key pillars in AMR R&D: a clinical trials network (CLIN-Net), a microbial surveillance database (LAB-Net), a clinical trials design suite (STAT-Net) and an epidemiological network (EPI-Net). These pan-European platforms have created a core information centre that facilitates antibiotic R&D and makes findings accessible to all ND4BB partners.

Figure 10 Breakdown of the New Drugs for Bad Bugs projects[42]



DRIVE-AB stands apart from the other ND4BB programmes as essentially a think tank group. Started in October 2014, DRIVE-AB is a partnership of 16 academic partners and seven pharmaceutical companies with a budget of just under €11 million.[43] The group is incrementally building evidence for detailed, new economic incentives to stimulate greater antibiotic innovation. To date, regarding innovation incentives, it has validated the principle bottlenecks to antibiotic innovation, performed an analysis of incentives from other industries that may be applicable for antibiotics and short-listed the most promising economic incentives. Since DRIVE-AB publishes its core results in peer-reviewed journals, there is a delay in making these findings fully available. However, the project is on schedule to deliver its final policy recommendations in the second half of 2017 (personal communication, Dr Stephan Harbarth, DRIVE-AB Project Leader, 2016).

The second iteration of the IMI – IMI2 – is currently being rolled out with funding from Horizon 2020. IMI2 aims to build on the successes of the IMI and will run for the period of 2014 to 2024 with a joint EC/EFPIA budget of €3.276 billion.[44] The IMI2's strategic research agenda outlines AMR as a key research priority and the IMI2 is expected to build on the ND4BB programme (personal communication, Dr Angela Wittelsberger, Scientific Officer, Innovative Medicines Initiative, 2016).[45] Many of the ND4BB projects have only just been started and are slated to run until 2020.

Analysis: The ND4BB programme is a comprehensive and well-established mechanism for supporting antibiotic R&D. It targets all aspects of the antibiotic value chain. The COMBACTE programme is particularly commendable and has established key R&D resources in Europe (e.g. CLIN-NET, LAB-Net and EPI-Net) that form the basis for additional drug discovery and development programmes. The IMI PPP model employed throughout ND4BB seems to be effective at pooling resources, facilitating collaboration among key stakeholders in the development process, and sharing the financial risk of R&D outlays across both the private and public sectors. However, given the nature of the IMI's partnership model between the EC and EFPIA, the ND4BB programmes primarily engage larger pharmaceutical companies and not SMEs. ENABLE is an exception and uses an innovative, flexible model targeted specifically at early discovery programmes of SMEs and academia. Additionally, DRIVE-AB has fostered the creation of the BEAM Alliance and advocated for the inclusion of SMEs in IMI2 projects as Associated Partners. The group's policy recommendations will likely result in the implementation of new antibiotic R&D incentives in the future. While DRIVE-AB provides an important and complimentary role to the clinically focused ND4BB programmes, it does not provide any incentives to antibiotic developers.

■ InnovFin Infectious Disease Finance Facility

Overview: "InnovFin: EU Finance for Innovators" is a joint project launched in 2014 by the European Investment Bank (EIB) Group and the EC under its Horizon 2020 framework programme.[46] InnovFin builds on its FP7 predecessor, the Risk-Sharing Financing Facility, and is comprised of a series of financing tools and advisory services for innovative enterprises of all sizes. By 2020, it is expected that InnovFin will provide over €24 billion in debt and equity financing to research and innovation focused European companies. Under this set of financial instruments a new finance facility for infectious diseases, InnovFin Infectious Diseases (InnovFin ID), was launched in June 2015.[47] The InnovFin ID aims to stimulate investments in the development of innovative vaccines, drugs, medical and diagnostic devices and novel research infrastructures for infectious diseases. Through InnovFin ID, the EIB provides loans between €7.5 million and €75 million via financial products ranging from standard debt instruments to risk sharing agreements. InnovFin ID targets validated projects that have moved beyond the preclinical stages of development and are looking to progress through the clinical stages. An Eligibility Committee comprising relevant EC officials reviews the submitted projects.

Analysis: InnovFin ID incentivizes R&D in the area of infectious diseases, including R&D on antimicrobials and AMR, through late-stage push funding in the form of low-risk loans and risk sharing programmes. InnovFin ID funding is available to large pharmaceutical companies, SMEs, research outfits and universities, non-profit entities and special purpose vehicles. InnovFin ID is an innovative mechanism for providing access to funding that also tries to minimize public financial risk. InnovFin ID funds up to half (on average 33%) of the project costs with the recipients funding at least 25% and third parties funding the remainder. Should the project fail, the loan essentially becomes a grant.

However, the condition that eligible projects must have surpassed the preclinical phase of development may hinder the participation of SMEs, which often struggle to reach the clinical phases.[48] Furthermore, the loan sizes may be insufficient support for smaller firms who may not be able to raise enough additional capital to cover the high costs of clinical tests. As noted above, clinical development of one drug candidate often costs upwards of €120 million. Another aspect to consider is that project proposals are put forth by industry and may not necessarily reflect an established priority setting framework. The InnovFin ID Eligibility Committee could be improved by including experts from the JPIAMR, in order to ensure that projects are selected based on an international AMR agenda.

■ European Medicines Agency

Overview: As the central drug regulatory body for the EU, the European Medicines Agency (EMA) is responsible for the market authorization of antibiotics submitted through their centralized procedure on behalf of the European member states. As a core TATFAR member, the EMA is working closely with the US FDA to standardize an effective protocol for the market approval of high priority antibiotics, alternative medicines and rapid diagnostic tools.[49] The EMA is able to employ a number of regulatory tools to expedite the market approval of novel antibiotic drugs such as offering scientific advice and protocol assistance to pharmaceutical companies, accelerating assessment of new drug applications and granting conditional market authorization for drugs that meet unmet medical needs.[49] Furthermore, the EMA has released an "Addendum to the guideline on the evaluation of medical products indicated for treatment of bacterial infections."[50]

Under this revision the EMA can authorize new antibiotics that address an unmet medical need related to AMR based on abbreviated, but targeted clinical development scenarios. Finally, it is interesting to note that the EMA is currently exploring the scientific and regulatory issues of bacteriophage therapy, which is not currently authorized in Europe as a medicinal product.[51]

Analysis: The EMA can use multiple lego-regulatory pull mechanisms to facilitate market approval of antibiotic drugs that address AMR. Expedited approval pathways as well as access to the EMA's scientific resources can help lower the cost of developing antibiotics.[1] In addition, earlier market entry may improve the revenue potential of a novel antibiotic as the developer can take advantage of a longer effective market exclusivity period. From a public health perspective, faster approval periods for antibiotics can increase access to needed antibiotics. However, this authorization speed and flexibility may come at the cost of ensuring a high standard of safety and efficacy for approved drugs through this pathway.[30] Lastly, SMEs often find that these lego-regulatory pull mechanisms do little to help them move through the expensive clinical phases of development.[1,30]

4.3 Key national initiatives that foster R&D of antibiotics

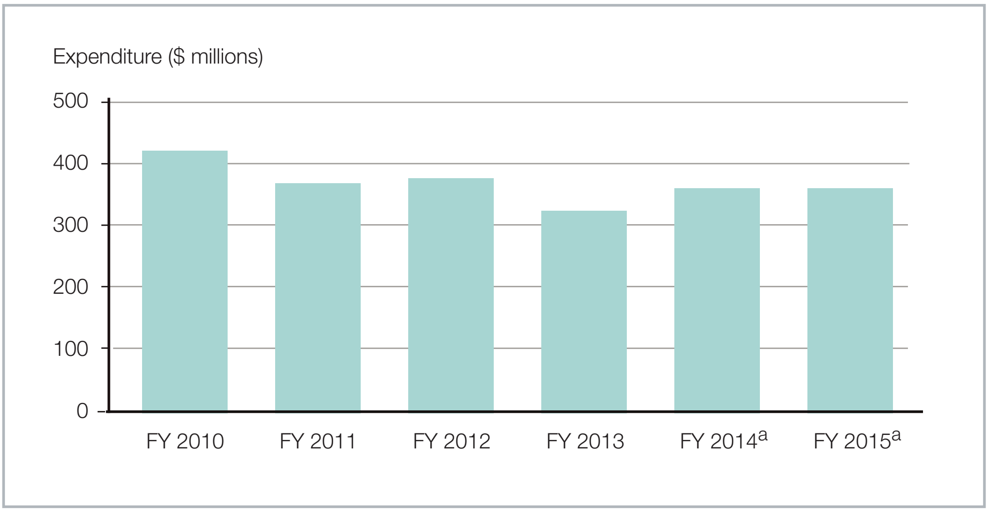
4.3.1 United States of America

■ *National Institute for Allergies and Infectious Disease, National Institutes for Health*

Overview: The National Institute for Allergies and Infectious Diseases (NIAID) conducts and supports basic and applied research to better understand, treat and prevent infectious, immunologic and allergic disease. The NIAID is the primary government agency within the US National Institutes for Health (NIH) that funds AMR R&D. In 2015, the NIAID had a budget of approximately $4.4 billion.[52] The Division of Microbiology and Infectious Diseases is the department within the NIAID that is responsible for providing funding opportunities and resources for researchers that support basic research, preclinical development and clinical evaluation of antibiotics. In a 2015 *Health Affairs* article, Outterson et al. note that annual NIH funding for AMR research has been steady since 2010 at approximately $350 million (Figure 11).[14] Unfortunately, this figure cannot be further separated to show how much goes towards antibiotic R&D.

In 2013, the NIAID provided a $62 million grant over 6.5 years to establish the Antibacterial Resistance Leadership Group (ARLG).[53] Led by the Duke Clinical Research Institute, ARLG develops, designs, implements and manages a clinical research agenda to increase knowledge of AMR. The Group is particularly focused on building transformational trials that will change clinical use of antibiotics. Some of their approaches involve earlier clinical evaluation of new antibacterial drugs and modernization of clinical trial testing strategies.

Figure 11 NIH research spending on AMR research, United States, fiscal years 2010–15[14]



a FY 2014 and FY 2015 are estimated by Outterson et al.

Another interesting initiative is the Antimicrobial Resistance Rapid, Point-of-Care Diagnostic Test Challenge.[54] Co-sponsored by the NIH and the Biomedical Advanced Research and Development Authority, the 2015/2016 Challenge is a prize competition of up to $20 million for the delivery of a diagnostic tool that can quickly identify bacterial infections in a clinical setting. The FDA and the Centers for Disease Control and Prevention (CDC) will provide the required technical and regulatory expertise for the evaluation process.

Analysis: The NIAID is the largest US government funding body for antibiotic R&D from basic research through clinical development. The vast majority of funded projects seem to be individual basic research projects through university grants and academic fellowships. In addition, the NIAID provides access to its vast network of R&D infrastructure, scientific expertise, and public and private partners. The ARLG is an example of a smaller faculty within the NIAID that coordinates the use of these resources and has multiple projects in the pipeline. The NIAID's pipeline levers are heavily push based, which is particularly appealing to smaller private firms, academic research groups and NGOs. The diagnostic prize is a notable step towards using outcome-based pull mechanisms to entice firms with the resources and capital to successfully develop a diagnostic product through to commercialization. However, it remains to be seen if the prize of $20 million is a large enough incentive to overcome the significant development costs.

■ *Broad Spectrum Antimicrobials Program, Biomedical Advanced Research and Development Authority*

Overview: The Biomedical Advanced Research and Development Authority (BARDA) is a government organization within the US Department of Human and Health Services. BARDA is tasked with enhancing development and purchasing of critical vaccines, drugs, therapies and diagnostic tools intended for public health emergencies. Arising from the growing concern for AMR and the lack of antibiotic innovation, BARDA established the Broad Spectrum Antimicrobials (BSA) Program in April 2010. The BSA Program's mission is "to help revitalize the antimicrobial pipeline by forming innovative public-private partnerships with companies engaged in antimicrobial therapy development."[55] Much like other initiatives within BARDA, the BSA Program provides non-dilutive funding and expert support throughout the stages of a drug's clinical development. The BSA Program's budget is determined annually. Their 2016 fiscal year budget has been awarded $182 million, over double the previous year's budget of $79 million.

Since the programme began five years ago, they have assisted four candidate antimicrobials from preclinical stages to Phase III clinical trials and another candidate to late stage Phase I clinical trials.[55] The programme's success is reflected in expected new drug applications from these projects; one is to be filed in April 2016 and another in 2017 (personal communication, Dr Joe Larsen, Deputy Director, BARDA Division of CBRN Medical Countermeasures, 2016). In addition, the BSA Program has setup flexible cost-sharing partnerships with GlaxoSmithKline and AstraZeneca that encompass a portfolio of candidate antimicrobials. The GSK/BSA partnership has funding of $200 million over five years ending in 2018 and has so far resulted in one candidate being progressed to Phase II clinical development and another lead clinical candidate that targets gram-negative bacteria being identified.[55,56] The AstraZeneca/BSA partnership, which started in 2015, has funding of up to $170 million over its five-year contract.[57] This partnership currently has one candidate in its portfolio and is in Phase III. Notably, the IMI-ND4BB is contributing funding for the EU clinical trials for this drug through their COMBACTE-CARE programme.

In the US National Action Plan for Combatting Antibiotic Resistant Bacteria, one of the strategic objectives was to create the Antibiotic Resistance Biopharmaceutical Incubator to improve the number of candidate molecules in the development pipeline.[58] This incubator, operated by BARDA and the NIH, would build on the BSA Program's flexible portfolio partnership model to create a consortium of key stakeholders that could pool funding, expertise and resources into the higher risk initial stages of drug development. The idea would be to further de-risk innovative research necessary to produce candidates with novel approaches to combating resistant gram-negative bacteria. Providing early stage funding allows innovative research to be validated enough for other sources of investment to participate: venture capital funds, governmental organizations like BARDA, or NGOs and charities. Competition for funding from the incubator has already commenced ahead of schedule with awards anticipated for 2016.

Analysis: BARDA's PPP incentive model is particularly targeted at the preclinical and clinical development barriers of antibacterial drugs. This synergistic approach appears to be effective given their success in progressing several drug candidates to market authorization assessment. The significant committed funding behind the GSK and AstraZeneca partnerships is promising and the flexible nature of these two collaborative portfolios is a welcome departure from the more bureaucratic process of typical government R&D funding. The portfolios allow the BSA and major pharmaceutical companies to quickly determine the viability of a particular project and either add or drop the project from the portfolio, thus reducing risk exposure and cost. The biopharmaceutical incubator programme will help BARDA apply its model to earlier basic research and hopefully provide a transitional link to the clinical phases of antibiotic development. This incubator may allow BARDA to appeal more readily to SMEs, which have not been well integrated into BARDA's partnerships. Finally, BARDA's focus on defensive and emergency related drugs may limit the scope of its antibiotic R&D agenda. However, under the Project Bioshield Act, BARDA has the capacity to administer AMCs for the procurement of products to be stockpiled for emergency use. While BARDA has not used this contracting mechanism for antimicrobials to date, it could be modified to provide a pull incentive or even support a delinkage approach (personal communication, Dr Joe Larsen, Deputy Director, BARDA Division of CBRN Medical Countermeasures, 2016).

■ *Food and Drug Administration*

Overview: The US FDA is a federal agency of the US Department of Health and Human Services. It collaborates with partners to address the issue of antibiotic resistance. It aims to ensure development of new strategies including novel antibiotic development and diagnostic devices. The FDA collaborates with external partners to advance clinical trials.

The agency is responsible for the market authorization of antibiotics in the US and uses a number of regulatory tools to support their development. Some of these levers are available through the implementation of the GAIN Act, which was ratified in 2012 as part of the Food and Drug Administration Safety and Innovation Act.[49,59] The GAIN Act allows Qualified Infectious Disease Product (QIDP) designations to be granted to unique molecules. These QIDP designations allow priority review of molecules as well as fast-track designation, allowing early consultation between the FDA and antibiotic sponsors. They may also allow an additional five years of market exclusivity.

The FDA has also created a multidisciplinary antibacterial task force to prioritize antibiotic development. This is a collaborative approach involving researchers within the FDA and as well stakeholder groups involved in antibiotic development.[60] Within the task force there is a focus on improving efficiency of clinical trials to aid antibiotic development.

A further initiative proposed is a Limited Population Antibacterial Drug (LPAD) programme under the 21st Century Cures Act.[61] This would provide the FDA with a new approval pathway to streamline the process of antibiotic development to allow access to antibiotics to patients with serious bacterial infections who lack appropriate treatment options. These antibiotics would be studied in smaller clinical populations and would establish safety and effectiveness for a limited population (i.e. not generalizable to the patient population as a whole).[62]

Analysis: These initiatives described are acting as pull incentives, specifically lego-regulatory strategies, to accelerate novel antibiotic development. By granting QIDP designations to unique molecules, the GAIN Act encourages alignment between regulatory agencies and industry and improves the market attractiveness of antibiotic development. This targets the latter stages of the antibiotic value chain (market approval and commercialization).[19] Overall this aims to speed up the antibiotic development process, accelerating access to novel antibiotics. While this should encourage participation by large pharmaceutical companies and improve the NPV, it may not benefit SMEs who might lack the capital reserve required to reach the clinical trial assessment stages.

The option of offering an additional five years of market exclusivity may further encourage participation of large pharmaceutical companies who could recover R&D costs through increased sales. But, it is worth noting that the high prices associated with extended intellectual property rights may further burden the health system and limit patient access.[30] There is added concern that a five-year extension of market exclusivity may not translate into efficient improvements in NPV due to the time discounting effect.[63]

By focusing on efforts to improve clinical trial efficiency the multidisciplinary task force can target the clinical development stage. It also aims to facilitate synergy and cooperation between stakeholders.

The accelerated approval pathway offered by LPADs under the 21st Century Cures Act would speed up the process of antibiotic development and access for those with urgent need, but there is a possibility that this could compromise safety and efficacy.[30] Some criticisms of this proposal include concerns regarding the methods used to speed up this process.[64] Much like the EMA's adaptive licensing pathway, the FDA would need to consider non-traditional study design and data analysis methods in order to be more flexible and accelerate drug approval. This leads to concerns regarding efficacy and safety as data may be drawn from different sources including small studies or Phase II clinical trials. While the antibiotics would be labelled accordingly with disclaimers, there is no guarantee that they would only be prescribed to the limited group of patients they are intended for.

These initiatives certainly offer incentives to accelerate the process of developing antibiotics for clinical use by targeting the latter stages of the value chain and encouraging large pharmaceutical companies to participate. However, as they only materialize in the final stages of antibiotic development, SMEs may be unable to participate if they lack the capital reserve to reach the later clinical study phases.

4.3.2 Canada

■ *Institute of Infection and Immunity, Canadian Institutes of Health Research*

Overview: The Canadian Institutes of Health Research (CIHR) offers opportunities for funding within health research.[65] The CIHR has invested C$93.8 million (Canadian dollars) between 2009/2010 and 2013/2014 in AMR research, of which C$15 million was in 2013/2014. Within the CIHR, the Institute of Infection and Immunity (III) supports research and helps to build capacity in the areas of infectious diseases and the body's immune system. The CIHR-III 2013–2018 Strategic Plan has made AMR a priority area for research. Previous projects have included the development of a surveillance programme, monitoring bacterial infections and antibiotic use. The CIHR-III is an active member, research collaborator and funder of the JPIAMR.

A couple initiatives have been developed specifically targeting the area of antibiotic resistance. The Novel Alternative to Antibiotics (NAA) Funding Opportunity aims to increase research funding available.[65] This initiative started in 2006 and is currently ongoing with total funding of C$13 million. Through open competitions it aims to encourage applications that are focused on novel approaches to antibiotic resistance. It combines input from 26 different partners including academia, industry, government and NGOs. As a result of this initiative, new antibiotics have been identified and several patents have been filed. A further initiative includes a partnership between Canada and the UK's Medical Research Council, which was established in 2007. Under this collaboration, a four-year joint grant on antibiotic resistance was launched in 2010. The CIHR contributed C$4 million. This grant allowed the funded teams to create partnerships and secure additional funding.

Analysis: In general, Canadian AMR initiatives tend to focus on other aspects of combating AMR than antibiotic R&D. The few antibiotic R&D initiatives offered by the CIHR-III act as push incentives, targeting the antibiotic value chain at the basic research level. By offering scientific grants and fellowships it promotes AMR science as a priority research area. In addition, by combining input across the private and public sector, the NAA Funding Opportunity may help to translate research into the preclinical development stage. The collaborative approach, both across the public and private sector and between Canada and the UK, does facilitate synergy and cooperation within the antibiotic market.[19]

4.3.3 United Kingdom

■ *UK Medical Research Council*

Overview: The Medical Research Council (MRC) is a publicly funded governmental organization, which coordinates and funds research in the UK. The MRC had a total budget of £771.8 million in 2014/2015.[66] It is working to address the key challenges in AMR in a multidisciplinary approach through three key national initiatives: the Antimicrobial Resistance Funders Forum (AMRFF), the Tackling AMR – UK Cross

Council Initiative and the UK Clinical Research Collaboration/Translational Infections Research Initiative. The MRC also represents the UK in the JPIAMR.

First, the Antimicrobial Resistance Funders' Forum (AMRFF) coordinates research councils, health departments, government bodies and charities and provides a forum to share information on AMR.[67] Second, the Tackling AMR – UK Cross Council Initiative is a new inter-disciplinary programme initiative started in 2014 that focuses on cross-resistant bacteria of humans and animals.[68] The Cross Council Initiative has four main themes to its strategy: (1) understanding resistant bacteria, (2) accelerating therapeutic and diagnostics development with collaboration between academia and industry, (3) understanding the complexity of the environment in AMR emergence and transmission and (4) understanding behaviour within and beyond the health care setting. This initiative offers a range of direct funding from small innovation grants (<€1 million) to large collaborative grants (€2–3 million). Finally, The UK Clinical Research Collaboration/Translational Infection Research Initiative (UKCRC TIRI) aims to promote infection research by encouraging multi-disciplinary collaboration, improve research infrastructure and promote human resource development.[69] With funds of up to £16.5 million, the UKCRC TIRI offers consortium grants to support new research partnerships and strategy development grants to foster new partnerships and improved research bids.

With funding support from the Newton Fund, the MRC has also initiated several major antibiotic R&D projects in developing countries. There is the UK-China AMR Partnership Initiative, which will fund research projects that address clinical and veterinary aspects of AMR in China. The UK will contribute £4.5 million and the National Natural Science Foundation of China will contribute ¥3 million. The MRC is also collaborating with the Government of India's Department of Biotechnology to establish two new AMR centres: The Cambridge-Chennai Centre Partnership on Antimicrobial Resistant Tuberculosis and The UK-India Centre for Advanced Technology for Minimising the Indiscriminate Use of Antibiotics. Nearly £7 million will be jointly invested by the UK and India. Both centres will work to develop new diagnostic tools and new treatment options for resistant infective diseases.

Analysis: The MRC's initiatives use push incentives to encourage and accelerate antibiotic R&D. They predominantly target the early to middle stages of the antibiotic value chain (basic research, preclinical and clinical development levels). The MRC has particularly concentrated on fostering multidisciplinary and interdisciplinary relationships that breakdown the traditional health science R&D silos. Their collaborative approach encourages the sharing of information and R&D resources between relevant stakeholders, and fosters partnerships between academia and industry. Moving beyond UK borders, the joint MRC/Newton Fund projects with China and India form valuable scientific relationships and resource channels between the UK and two low- and middle-income countries (LMICs), where a significant portion of AMR health burden exists. The MRC/Newton Fund projects address some aspects of high-priority medical need and antibiotic stewardship.

■ *Review on Antimicrobial Resistance*

Overview: The Review on Antimicrobial Resistance by Jim O'Neill was commissioned by the UK Prime Minister, David Cameron, in 2014 to explore global solutions to AMR.[5] It is also funded by and supported by the Wellcome Trust, an independent global charity. To date, numerous reports have been published encouraging innovation in antibiotic development and in the development of rapid point-of-care diagnostic tests. The review recommends greater funding to support early-stage R&D activities. It suggests a Global Innovation Fund for AMR of $2 billion over five years with support from the global pharmaceutical industry.

The AMR Review recommends market entry rewards for successful new antibiotics that meet priority indications. It estimates that $15–35 billion is required to achieve about 15 licensed new drugs over the next 10 years. This would include two new broad-spectrum classes of antibiotic and two newly targeted therapeutic classes every decade. It works with key stakeholders to determine R&D pipeline lever solutions. The AMR Review final package of recommendations will be available by the summer of 2016.

Analysis: Initiatives proposed by the O'Neill Review could act as both push and pull incentives.[48] By recommending early stage investment as well as later stage lump payments, these initiatives target all stages of the value chain. The investments are realistic in scale for antibiotic development. Offering market rewards would target the later stages of market approval and commercialization and these late stage payments would help to delink the volume of antibiotics sold from industry revenues. These investments could improve the NPV of antibiotic projects and as such could encourage participation of pharmaceutical companies.

A global innovation fund, with contributions from the pharmaceutical industry, would help to support early stage research and may encourage participation of SMEs in the antibiotic development market.[48] The AMR Review's suggested $2 billion fund is a realistic proposal for the costs that would be required. A further proposal is for the harmonization of the regulatory approval process across countries which would encourage synergy and cooperation in the antibiotic market. The AMR Review also recommends increasing information sharing during the early development stage. This could be of benefit to both SMEs and large pharmaceutical companies by reducing the regulatory burden and the overall costs of antibiotic development. SMEs and larger pharmaceutical companies may be willing to share information to differing degrees. While the AMR Review offers a framework of how to tackle the issue of AMR on a global scale, the initiatives may be challenging to implement across a global market and may require considerable political effort to coordinate regulatory requirements across countries.

Longitude Prize

Overview: The Longitude Prize is a monetary reward offered by Nesta, a British lottery-funded charity.[70] It was announced by the UK Prime Minister David Cameron in 2012 and opened for submissions in 2014. There is a £10 million prize to develop a new diagnostic tool to identify when antibiotics are necessary.

Analysis: This R&D end prize is a pull incentive that rewards the development of a successful diagnostic test. It targets the commercialization stage of the value chain and offers a substantial monetary prize. It remains to be seen whether this sum is an adequate incentive to pull a diagnostic tool to market.

4.3.4 France

French National Research Agency

Overview: The French National Research Agency (ANR) was established by the French Government in 2005 to fund basic and applied research projects in all science fields.[71] It provides funding via grants to public research organizations, universities and private companies including SMEs. In the field of AMR research it closely collaborates with the JPIAMR.

Analysis: By providing funding via grants to both public and private companies, the ANR is utilising push incentives to encourage antimicrobial resistance R&D. This also may allow participation of SMEs that have limited capital reserve to enter the antibiotic market.

French National Institute of Health and Medical Research

Overview: The French National Institute of Health and Medical Research (Inserm) was founded in 1964 as the only French public research institute to focus entirely on human health.[72] It has forged close partnerships with other public and private research establishments. Inserm's Institute for Microbiology and Infectious Diseases (IMMI), with support from AstraZeneca (€500,000), launched a call for two proposals on antibiotic resistance in January 2014.[73] One proposal focuses on the ultra-rapid diagnosis of resistance and the other on the identification of novel targets for antibiotics. Two projects have been selected.

Inserm (Transfert), an incorporated subsidiary of Inserm, focuses on adding value and reducing risk for innovative projects at pre-commercial stages, bridging the valley of death.[72] Inserm (Transfert) can provide developers with high-potential antibiotic candidates access to expert partners and an international R&D consortia to help push the project through the clinical phases of development.

Also, Inserm co-founded, with other research institutes, the National Alliance for Life and Health Sciences (AVIESAN) to strengthen coordination between national research institutes, universities and hospitals. Since January 2015, it has been coordinating research in areas of infectious disease and microbiology.[53]

Analysis: The antibiotic R&D initiative led by IMMI, with support from AstraZeneca, focuses on basic research but there is also the possibility of translating this research into the preclinical development stage. Inserm (Transfert) focuses on reducing risk at pre-commercial stages and offers a variety of push incentives to early-stage life sciences companies that need support across the preclinical valley of death. This encourages greater participation from SMEs. The development of strong collaboration between public and private partners, and the support of a large pharmaceutical company, facilitates cooperation and synergy across the antibiotic market. AVIESAN encourages collaboration with industry, which facilitates synergy across the antibiotic market and may encourage participation from pharmaceutical companies.

4.3.5 Germany

■ *German Federal Ministry of Education and Research*

Overview: The German Federal Ministry of Education and Research (BMBF) represents Germany at the JPIAMR and has established two key national programmes that tackle AMR: the German Centre for Infection Research (DZIF) and InfectControl 2020.

Established in 2011, the DZIF aims to tackle the most urgent challenges in infection via an integrative approach.[74] The aim is to ensure collaboration between universities, university medical centres, Leibniz and Max Planck institutes, Helmholtz centres and other government research establishments. In total it is an affiliation of 35 research institutes located at seven sites distributed throughout Germany. DZIF has formed Thematic Translational Units of scientists, each dedicated to one specific pathogen or infectious disease. There are specific research areas focused on faster molecular diagnostics and the development of new vaccines and antibiotic drugs.

InfectControl 2020 is a consortium of representatives from academia and enterprises that encourages cooperation between scientists and industry in collaboration with patient associations and the general public. It aims to develop solutions regarding the threat of AMR on a national and global level.

Analysis: Both DZIF and InfectControl 2020 aim to provide a collaborative approach to overcoming AMR. This may bridge the gap between basic research and antibiotic drug development and may go some way to overcoming the challenges at the preclinical development level or the 'valley of death'. This integrative approach should encourage the participation of larger pharmaceutical companies and also facilitate synergy across the antibiotic market.

■ *German Research Foundation*

Overview: The German Research Foundation (DFG) is a research-funding organization serving all branches of science and humanity.[75] It currently supports a number of research projects on the subject of antibiotics within the field of basic research, providing funding through individual grants.

Analysis: The DFG's antibiotic R&D initiatives act as push incentives, targeting the value chain at the basic research level and may allow specific priorities to be targeted. An issue with these types of incentives is that tangible results are not always realized and it can be difficult to translate research into drug development.

4.3.6 Netherlands

■ *Netherlands National Centre for One Health*

Overview: Utrecht University, UMC Utrecht and Wageningen UR founded the Netherlands National Centre for One Health.[74] It pursues basic and clinical research and allows collaboration between academia, research institutes, industry, policymakers and NGOs. It forms the basis for a high-quality consortium with top expertise in the field of AMR. It aims to better understand the emergence, transmission and dynamics of AMR and to improve and expand tools for AMR prevention and intervention.

Analysis: By pursuing fundamental research and allowing collaboration between academia and industry the Netherlands National Centre for One Health aims to target many levels of the antibiotic value chain including basic research, preclinical development and clinical development. This collaborative approach encourages participation of the pharmaceutical industry and facilitates cooperation and synergy across the antibiotic market.

■ *Netherlands Organization for Health Research and Development*

Overview: The Netherlands Organisation for Health Research and Development (ZonMw) funds and promotes research, development and implementation.[76] In order to help control AMR and to foster the development of new antimicrobials, ZonMw set up the research programme Priority Medicines Antimicrobial Resistance.[77] It will fund basic and applied research over a period of nine years (2009–2018) with a budget of €14.76 million. Five main research areas have been identified which include mechanisms and targets for new drugs and new technologies, in particular rapid diagnostics. Additionally, ZonMw represents the Netherlands in the JPIAMR and contributes to many of the initiative's strategic work packages.

Analysis: By funding basic and applied research ZonMw is providing a push incentive, targeting the earliest stage of the antibiotic value chain. This aims to overcome the discovery void with a sizeable budget.[19] However, there does not appear to be a clear avenue for ZonMw's drug discovery research to be translated into actual product development.

4.3.7 Sweden

■ *Swedish Research Council, Formas and Vinnova*

Overview: There are three major government agencies in Sweden that play a leading role in combating AMR and are responsible for supporting R&D of antibiotics. First, the Swedish Research Council (SRC) is a government agency which was established in 2001.[78] It provides funding for basic research in all disciplinary domains; antibiotic resistance is one focus area. It has a leading role within the JPIAMR, with the main secretariat being hosted by the SRC. Second, Formas is a national research council which receives funding from the Ministry of the Environment and Energy and the Ministry of Enterprise and Innovation in Sweden.[79] It provides funding for basic research, with antibiotic resistance being a key priority. Third, Vinnova is a Swedish government agency founded in 2001.[80] It is the expert agency in innovation and funds needs-driven R&D within strategically important areas, including antibiotic resistance.

Analysis: All three of these government agencies provide funding through scientific grants and fellowships. They all provide push incentives that primarily target basic research, however, Vinnova does offer avenues for clinical development of qualified drug candidates. While these incentives encourage research focused on antibiotic resistance and may help to overcome the discovery void, they may not translate into marketable antibiotics. They can, however, complement other initiatives and benefit from public and private research collaborations.[19]

5. Discussion

Based on our case studies and initiatives analysis we formulated a series of key policy questions that deserved in-depth discussion. These questions are as follows:

1. How do current initiatives measure across the evaluation criteria?
2. What is the current balance between push and pull incentives?
3. What are our knowledge gaps in the antibiotics market?
4. What is the current level of coordination between and within initiatives?
5. What is the distribution of initiative support across the antibiotic value chain?
6. How are SMEs supported through existing initiatives?
7. Are public health needs, such as stewardship, patient access and medical priorities, reflected in the current set of initiatives?

This discussion forms the foundation on which we determined our final recommendations.

5.1 How do the current initiatives measure across the evaluation criteria?

Commendable steps are being taken to reinvigorate the antibiotic R&D pipeline at international, EU and national levels. This is clearly evidenced by the 58 active initiatives and sub-initiatives that directly incentivize the R&D of new antibiotics, alternative therapies, or diagnostic devices. In addition, we identified nine active initiatives that coordinate strategic actions on AMR (e.g. TATFAR, Global Action Plan, DRIVE-AB, etc.) and seven initiatives that have either been proposed or have yet to be fully implemented (e.g. Global R&D Facility, Fleming Fund, etc.). Our criteria-based analysis (Appendix 4) shows that there are important successes across the initiatives that provide direct incentives to antibiotic R&D (Table 8). However, these areas of strength can and must be improved on. Our analysis also highlights a number of significant gaps and weaknesses across the current set of initiatives.

Firstly, it is promising to see that all initiatives with direct incentives are working to improve the NPV of antibiotic R&D in some way. However, additional analysis highlighted that there is an imbalance in the number of push versus pull incentives used to improve antibiotic NPV (discussed in detail in section 5.2). Additionally, we found that there is an unequal distribution of incentives across the antibiotic value chain that favours early stage basic research (discussed in detail in section 5.5).

We are also pleased to see that the majority of initiatives recognize that cooperation and synergy is critical to improving the antibiotic development pipeline. But, it appears that there is insufficient coherence and coordination across and within these cooperative initiatives (discussed in detail in section 5.4)

Table 8 Summary of the criteria-based assessment of current initiatives and sub-initiatives that provide direct incentives for antibiotic R&D

Initiatives that:	Improve antibiotic R&D NPV	Enable participation of SMEs	Encourage participation of large cap firms	Facilitate cooperation and synergy	Promote antibiotic conservation and patient access	Target specific high-priority medical needs
International-level	5	1	1	5	2	5
EU-level	13	3	11	11	1	12
US	9	3	8	7	0	4
Canada	5	0	1	4	1	1
UK	11	2	1	6	3	4
France	4	1	0	4	0	2
Germany	5	2	2	4	3	3
Netherlands	3	1	1	3	2	3
Sweden	3	1	0	3	0	1
Total	58	14	25	47	12	35
Percentage of total	100.0%	24.1%	43.1%	81.0%	20.7%	60.3%

Note: It is challenging to separate broader initiatives from their sub-initiatives with regards to their differing roles in stimulating antibiotic R&D. Therefore, this table counts both the broad initiatives as well as any of their sub-initiatives. Evaluation criteria that were deemed unclear for a particular initiative or sub-initiative were omitted from this tabulation. Initiatives that indirectly support antibiotic R&D by coordinating strategic actions on AMR were also excluded from this tabulation because they generally meet all criteria.

Our analysis has also identified a number of weaknesses within the current set of initiatives. Incentives targeting SMEs are particularly lacking at international, EU and national levels (discussed in detail in section 5.6). It also seems that antibiotic stewardship and patient access policies are not well integrated into R&D initiatives (discussed in detail in section 5.7.1). Lastly, our research team had particular difficulty determining whether many R&D initiatives incorporated specific targeting of high-priority medical needs (discussed in section 5.7.2).

5.2 What is the current balance between push and pull incentives?

5.2.2 Incentives currently being used

Our analysis shows that there is currently an imbalance in how incentives are used to overcome the multitude of barriers facing antibiotic development. The vast majority (76%) of initiatives employ only push forms of incentivization (Table 9) and the bulk of funding follows these push-based initiatives. This is problematic given that a combination of push, outcome-based pull and lego-regulatory incentives are needed to effectively improve the entire antibiotic pipeline.[30]

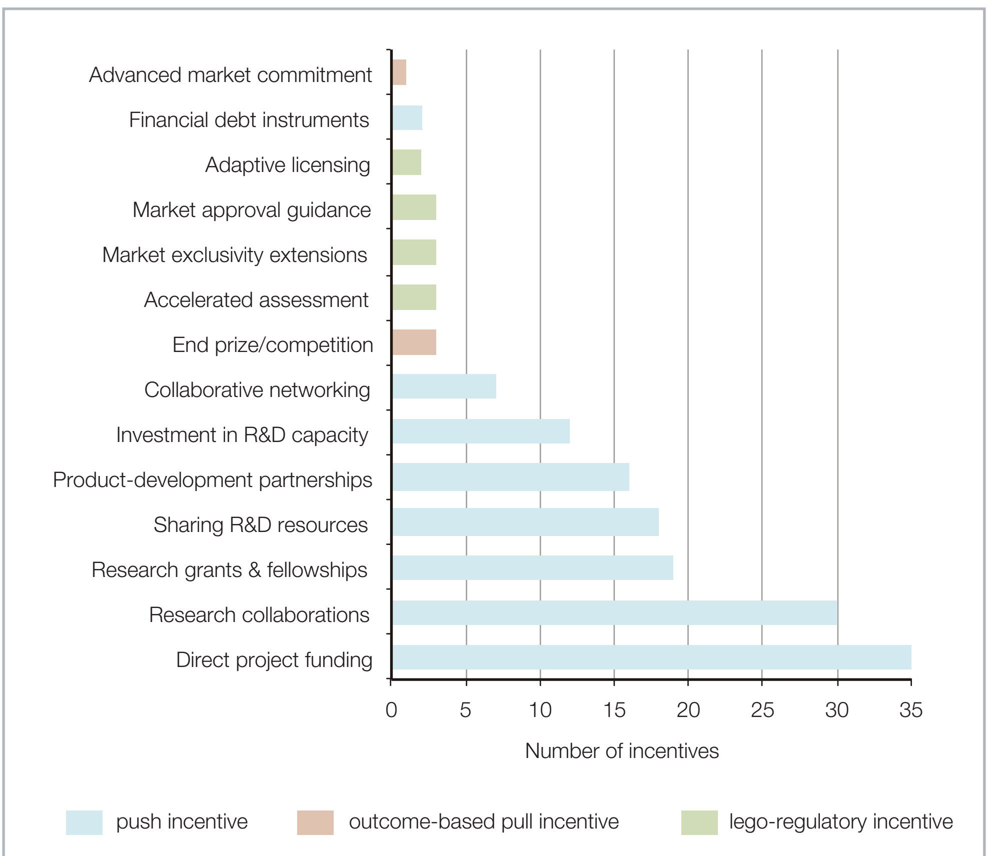
Table 9 Active initiatives and sub-initiatives based on their underlying incentives

Initiatives using:	Only push incentives	Only outcome-based pull incentives	Only lego-regulatory incentives	A hybrid of push-pull incentives	Only coordinate AMR action
International-level	5	0	0	0	3
EU-level	11	1	1	0	1
US	5	1	2	1	4
Canada	5	0	0	0	0
UK	10	1	0	0	1
France	4	0	0	0	0
Germany	5	0	0	0	0
Netherlands	3	0	0	0	0
Sweden	3	0	0	0	0
Total	51	3	3	1	9
Percent of total	76.1%	4.5%	4.5%	1.5%	13.4%

Europe and individual states are relying on the use of traditional methods of supporting R&D, which may not be sufficient in the case of antibiotics. Figure 12 shows that the top three most common incentives are direct project funding, research collaborations and research grants and fellowships for scientific personnel (see Appendix 5 for identification of incentives used by the initiatives). These are valuable incentives, however, as discussed in detail below, they heavily support the early stages of the antibiotic value chain. In contrast, end prizes, prize competitions and AMCs are rarely used, but effectively support the later commercialization stages required to bring an antibiotic into the market. Organizations such as the Global Alliance for Vaccines and Immunizations, also known as the Gavi Alliance, have successfully used pull mechanisms to incentivize development and marketing of drugs for neglected diseases.[81]

The ultimate goal is to link various push and pull mechanisms in a hybrid approach, recognizing that no singular method of incentivization will adequately stimulate antibiotic R&D alone.[30] As initially put forth by Brogan and Mossialos, a hybrid strategy would provide a tool for early investment and risk sharing, while also ensuring a credible purchase commitment and enticements for firms to actually bring novel antibiotics to

Figure 12 Distribution of incentives used by antibiotic R&D initiatives



market.[25] At present, there is minimal synchronization between the limited pull mechanisms available and the multitude of push mechanisms currently applied. Linking push and pull mechanisms will be particularly valuable for major initiatives such as the IMI, BARDA and InnovFin ID, which have the funding and coordination capability for such hybrid incentive strategies.

5.2.2 Incentives that are missing

Based on our assessment of the existing initiatives, there are several key incentives that are missing from the current arsenal, or are under utilized*. First, there are currently only three prizes offered in return for a marketable product. All three prizes target development of different rapid, point-of-care diagnostic tools – none target antibiotic drug development. The EC's prize offers €1 million, the UK's Longitude Prize offers £10 million and the US NIH's prize competition offers up to $20 million.

If an end prize were to target a novel first-in-class antibiotic, the AMR Review team estimated that the prize would need to be in the range of $1 to $1.5 billion.[5] This prize needs to be large due to time discounting and to make antibiotic investment competitive with other therapeutic fields. Given the great size of this prize, it would likely need to be offered and managed by a global or European body. Beyond incentivizing antibiotic development, this prize could be used as a method of purchasing the antibiotic's patent and jointly procuring the drug on behalf of participating countries. Global procurement of novel antibiotics has the benefit of being able to prudently manage the antibiotic's volume and distribution. The AMR Review further estimates that a fund of $15 to $35 billion would be needed to develop 15 new drugs over the next 10 years.

Also, it appears that pricing and reimbursement incentives are missing from current antibiotic R&D initiatives. Aligning pricing and reimbursement schemes with the public health value that antibiotics provide is important to enticing investment in antibiotic R&D.[26] It appears that most countries include antibiotics within their wider pricing and reimbursement policies, which are often specifically tailored to reduce drug costs and procurement inefficiencies. The downward pressure on the prices of antibiotics, which are often lumped together with other drugs, does not reflect their true value. We recognize that national pricing and reimbursement strategies are highly contextual and reflect a country's individual health priorities and ability to pay. Yet, there still may be a role for medicines with high global health value, like antibiotics, to be priced and reimbursed separately from other health technologies. In conjunction, AMCs should be considered as a method of controlling the volume of antibiotics purchased at value-centred prices. Advanced market commitments could be used by multiple nations to jointly procure antibiotics and regulate the antibiotic's consumption. Without consumption controls, value-based pricing and reimbursement may lead to high and unnecessary public cost.

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* This list is not exhaustive and there are multiple other incentives that have been proposed. See Renwick et al.'s 2015 review for additional insight on other incentives.

Finally, through our analysis we did not identify any tax incentive policies that specifically benefit firms developing antibiotics and related products. Tax incentives can come in the form of tax credits, allowances, or deferrals that reduce a company's current tax liability.[30] In our opinion, there is a role for coordinated tax incentives in Europe that support firms developing antibiotics and potentially other global high priority medicines. Tax incentives do not require upfront payments by governments and can be tailored to benefit both SMEs and big pharmaceutical companies.

Financial incentives could be combined with clawback arrangements that recapture public funding once an antibiotic has successfully made it to market. For example, InnovFin ID debt instruments require project owners to repay the original loan plus interest if the project is successful. Such a clawback arrangement makes sense given that the public ultimately deserves a positive return on their financial investment. Funds generated from clawback agreements could even be reinvested in antibiotic R&D. In the context of taxes, clawbacks may take the form of tax deferrals that are recalled once an antibiotic makes it to market. Alternatively, the public could receive a return on their investment (ROI) through guaranteed lower prices on antibiotics that reach the market. Clawback arrangements such as this could also be linked with monetary push incentives such as milestone prizes or direct funding. This concept of linking antibiotic investment with future financial returns builds off of Brogan and Mossialos' Options Market for Antibiotics model.[25] Governments that invest early in antibiotic R&D can expect larger future clawbacks given that their investment is riskier than if they invested later in the R&D process.

5.3 What are our knowledge gaps in the global antibiotics market?

Based on our research, we have been able to gather a partial picture of the current antibiotics market. However, to further determine how best to improve the antibiotics pipeline, we need a comprehensive understanding of how much is being invested by private and public entities and what products are currently in development. Ultimately, we want to be able to determine ROI in terms of dollars spent and antibiotic pipeline progress. This will help public and private entities become more efficient with their investments.

5.3.1 Global antibiotic R&D investment

Based on Kelly et al.'s analysis of EU and JPIAMR national funding of antibacterial research, we can estimate that approximately €147 million* was annually invested between 2007 and 2013 by European public agencies into the R&D of antibiotics, alterative

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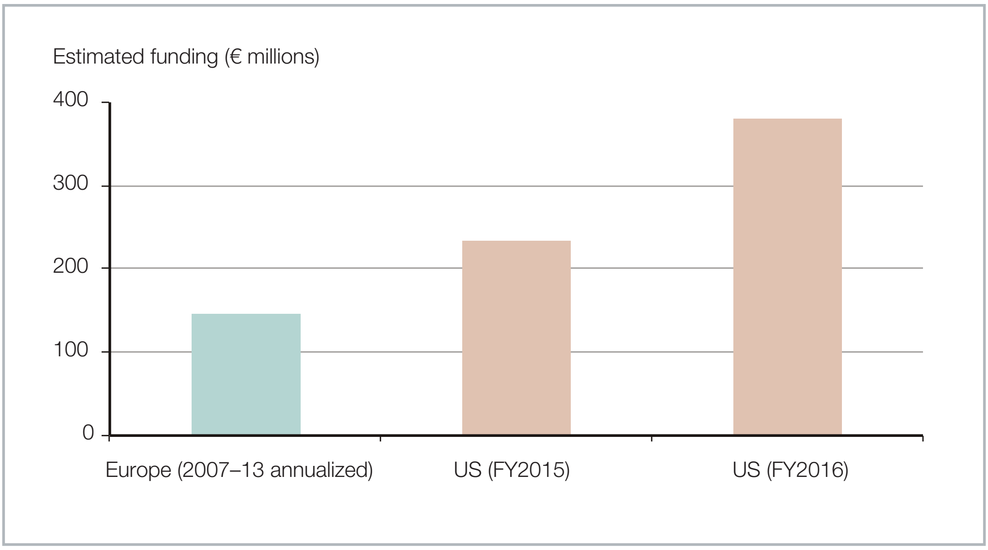
* This figure was calculated using data displayed in Kelly et al.'s 2015 *The Lancet Infectious Diseases* article. We summed the amounts invested at EU and national levels into antibacterial research related to therapeutics and diagnostics over the seven years 2007–13. The entire EC contribution to the IMI was also included in this figure, despite the IMI funding projects beyond therapeutics and diagnostics. We subtracted the national contributions of non-EU JPIAMR members (Canada and Israel) pulled from the author's original dataset. Between 2007–13 Canada contributed ~$68 million to therapeutic and diagnostic antibacterial projects ($9.8 million annualized) and Israel contributed $160,000.

Figure 13 Estimated annual public funding of R&D of antibiotics and related products, EU and the US[14,31,55]



therapies and diagnostics.[31] In contrast, we estimate that US government agencies invested approximately $260 million* (~€234 million) in antibiotic R&D in 2015.[55,82] The US investment in antibiotic R&D is expected grow substantially to $422 million (~€380 million) for 2016 with AMR budget increases to both the NIH and BARDA**. As can be seen, there is a significant difference in public funding of antibiotic R&D between Europe and the United States (Figure 13). However, it is unclear how the differences in public funding have affected outcomes in the antibiotic pipeline. Thus, there is a need for an ongoing assessment of ROI from public antibiotic funding. Missing in this picture are the antibiotic R&D investments made by other nations such as Japan, South Korea, China and India.

Private sector funding is the other part of the antibiotic R&D investment equation. However, we know little about how and how much the private sector is investing in antibiotic R&D. Commitments by private companies to public-private product

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* This figure was calculated using data from the NIH and BARDA, the two largest US government agencies funding antibiotic R&D. BARDA's FY2015 budget was $79 million. The NIH's FY2015 AMR budget was $361 million, half of which we assumed went towards R&D of antibiotics and related products. This assumption appears conservative given that approximately 84% of European public AMR funding is directed to either therapeutics or diagnostics. The 14 March 2016 USD:EUR conversion rate of 0.900 was used for the currency conversions.

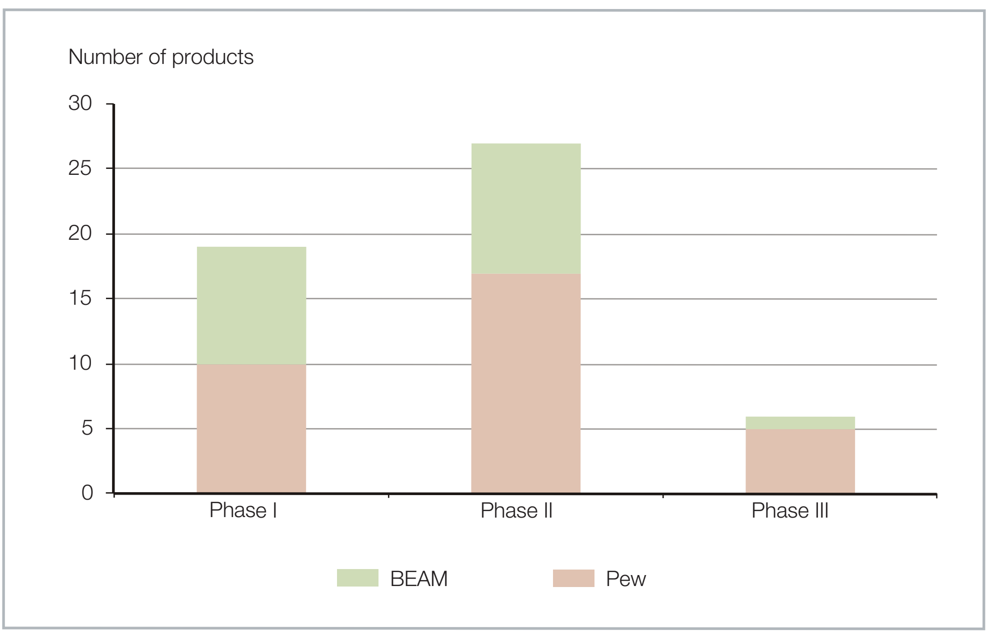
** BARDA's realized FY2016 budget has increased to $192 million (personal communication Dr Joe Larsen, Deputy Director, BARDA Division of CBRN Medical Countermeasures, 2016). The NIH has requested an increase of $100 million to its AMR budget in order better support the National Strategy for Combatting Antibiotic-Resistant Bacteria. Again, we estimated that half the NIH's AMR budget would go towards R&D of antibiotics and related products.

development partnerships (PDP) such as the IMI and BARDA likely only make up a small portion of private investment. Data on venture capital investment also only provides a snap shot of private investments into R&D projects. Based on 2008–13 data from the BIO report, $181 million was raised annually through venture capital for global antibiotic R&D. It is unclear to which firms (large pharmaceutical firms vs. SMEs) this venture capital money is heading. Further obscuring the picture is the lack of transparency in investments made by big pharmaceutical firms and SMEs into their own R&D operations.

5.3.2 The global antibiotic pipeline

Based on information gathered from the Pew Charitable Trusts and the BEAM Alliance we know that there are at least 19 antibacterial products in clinical development Phase I, 27 products in Phase II and 6 products in Phase III (Figure 14).[15,17] Using transitional success rates for antibiotic clinical development, this pipeline might translate into approximately six systemic antibiotics that have the potential to target gram-negative bacteria. This is promising. However, only one antibiotic in the entire pipeline uses a novel mechanism of action and it is specific to targeting Pseudomonas. Developing and marketing reiterations of existing classes of antibiotics will not overcome antibiotic resistance. Novel antibiotics are needed to provide more sustainable and effective methods of treating bacterial infections that are increasingly resistant to the current classes of antibiotics.

Figure 14 Partial picture of the current development pipeline of antibiotics and related products



Note: Compiled from data provided by the Pew Charitable Trusts and the BEAM Alliance.[15,17]

This pipeline analysis is not an accurate representation of the complete global antibiotic pipeline. We are missing US pipeline data on alternative therapies, European pipeline data from large pharmaceutical firms, and complete pipeline data from other countries such as Japan, South Korea, China and India. In addition, we have no information on the development pipeline of diagnostic tools.

Having a complete picture of the antibiotic pipeline allows us to determine how aligned the current pipeline is with global medical needs. Future investments can also be better targeted to support high-priority, high-value antibiotic R&D projects. Moreover, by having a better understanding of the antibiotics pipeline we can more realistically assess the predicted market outcomes from current R&D. For instance, the Infectious Disease Society of America has called for 10 new antibacterial drugs by 2020, yet we do not know how close or far we are to reaching this goal.[83]

The WHO is currently establishing a Global Health R&D Observatory that has the potential to act as a global data hub on antibiotics and other medicines. This observatory could collate and monitor information from around the world on R&D resource flows, product pipelines and research outputs in order to inform priority setting for future R&D investments. The WHO is currently seeking consultation on how to fully implement the Global Health R&D Observatory.[84]

5.4 What is the current level of coordination between and within initiatives?

5.4.1 Inter-initiative coordination

The antibiotic R&D initiative environment has become crowded.[85] At just the global level, the JPIAMR, TATFAR and EDCTP each actively strive to coordinate antibiotic R&D. The Global Action Plan on AMR and the G7's GUARD Initiative are global strategies that plan to additionally coordinate global antibiotic R&D. Thus, there is undoubtedly some overlap in these international initiatives' goals, strategies and activities.

There are also many valuable, smaller initiatives that are left out from these global coordinating networks. For instance, the JPIAMR does not leverage support from the UK's ANTUK, Wellcome Trust and BSAC; Germany's Leibniz Institute and Infect Control 2020; Sweden's Vinnova and Formas; and the Netherland's Centre for One Health. Of particular concern is the degree of coordination in clinical trials globally and across Europe. The EDCTP, BARDA and IMI are the largest antibiotic clinical trials programmes, but there are multiple other initiatives that support clinical trials at a smaller scale. This suggests that there is significant room to build synergies across the existing set of initiatives by further sharing and coordinating resources.

Therefore, there is a need for a single global governing body for antibiotic R&D. This entity would: set globally accepted priorities and targeting for antibiotic R&D; coordinate all existing and new initiatives and build synergies between all stakeholders; minimize global inefficiencies arising from overlapping antibiotic R&D work; and integrate antibiotic R&D efforts within the broader global AMR strategy. This global governing is not intended to stifle the diversity of approaches needed to stimulate antibiotic innovation, but rather provide a unified direction for these varying approaches. Additionally, a global governing body will be essential to any strategy that involves a large prize for successful development of a novel antibiotic and joint procurement of the antibiotic for multiple nations.

5.4.2 Intra-initiative coordination

Our analysis shows that a large number of initiatives are partnerships between two or more organizations, which benefit from sharing the risks and costs of antibiotic R&D. These partnerships vary substantially based on the number and type of organizations involved.

Public-private partnerships are the most common form and tend to be supported by significant funding. They can be single partnerships between a public agency and a pharmaceutical firm such as that of the BARDA/GSK joint portfolio programme. Alternatively, they may be multi-partnerships that bring together public agencies, academic institutions, NGOs and industry, such as the IMI. In our analysis, we have also observed private-private partnerships such as ANTUK and public-public partnerships such as the JPIAMR.

However, it is unclear which method of partnership is most effective for differing purposes. Single partnerships boast adaptability to changing scientific discoveries and market conditions. In contrast, large multi-organization partnerships can draw on a wide array of resources, but may be less flexible. Moreover, the various public and private organizations that could participate in such partnerships bring varying benefits and drawbacks. Therefore, we suggest that the role of antibiotic R&D partnerships be further explored in the near future.

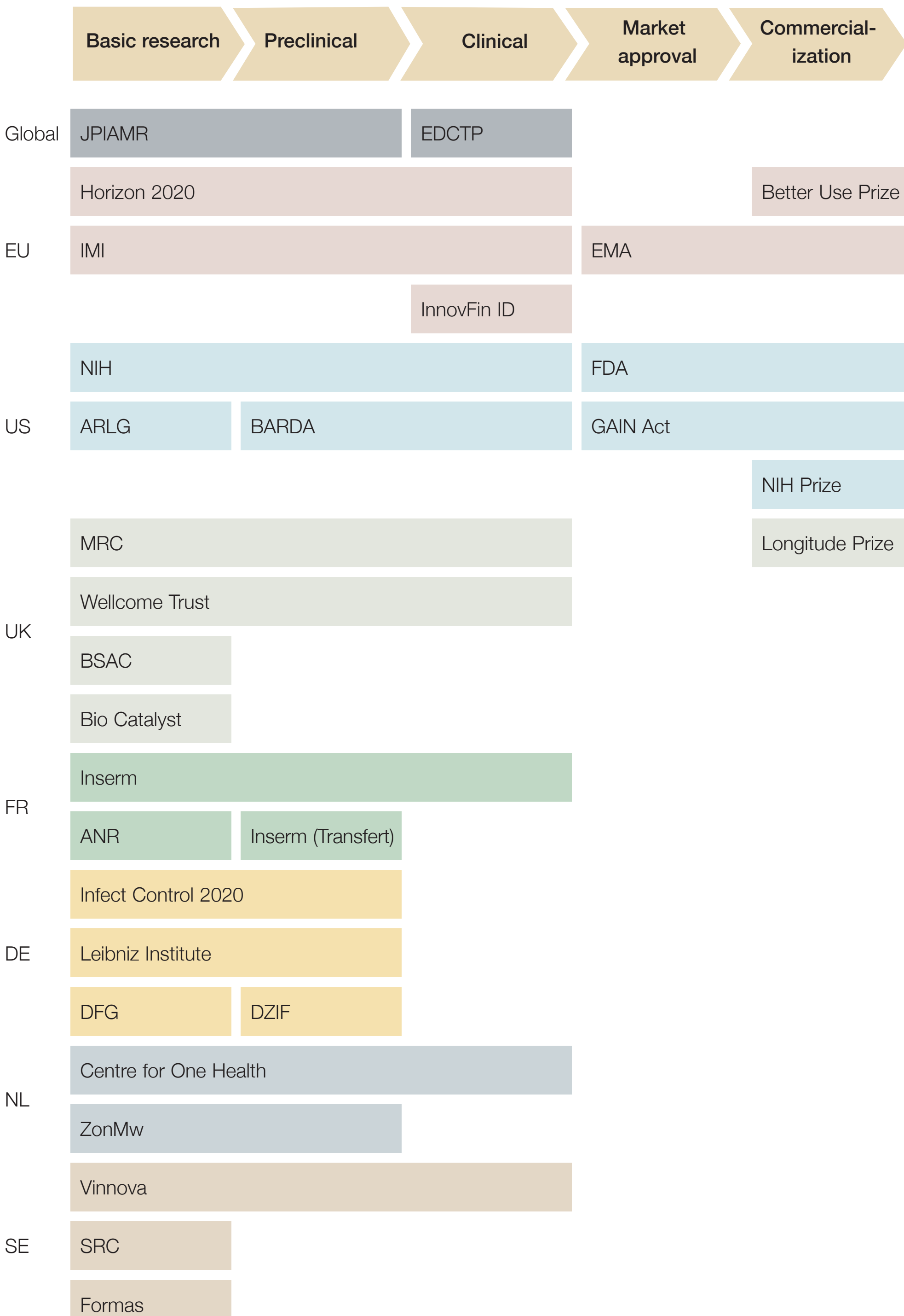
5.5 What is the distribution of initiative support across the value chain?

Our assessment shows that there is an unequal distribution of initiatives across the antibiotic R&D value chain (Figure 15). The following discussion section will explore this issue.

5.5.1 Basic research

A majority of European initiatives identified in this report target basic research of antimicrobials. This finding is reiterated in Kelly et al.'s analysis of European public funding of antibacterial research, which found that 86% of national-level public funding in antibiotic therapeutics was for basic research (therapeutic sub-categories I – II).[31,32] Basic research lends itself to being subdivided into multiple small projects that require lesser monetary commitments. In comparison, preclinical and clinical research tends to require

Figure 15 Distribution of international, EU and selected European national antibiotic R&D initiatives across the antibiotic value chain



far larger investments that cannot be easily parsed. Thus, from a political feasibility standpoint it is understandable why the majority of public funding goes towards basic research. While basic research is important in the development process, an overemphasis of funding towards early discovery stages might inhibit R&D progress of existing antibiotic candidates that could reach the market.

5.5.2 Preclinical and clinical trials

The majority of European public funding towards preclinical and clinical trials appears to come from the IMI. Despite having only nine active projects, the IMI has invested €312 million in EC public funding and €294 million in in-kind private sector contributions towards antibiotic clinical studies. The IMI has proven to be an excellent model for antibiotic development on multiple fronts.

First, the IMI's PDPs actively engage with the pharmaceutical industry to combine resources and expertise, as well as share financial risk. The PPP model of the IMI also acts to align private and public priorities. Second, the IMI's investment in European-wide clinical trial infrastructure allows researchers to access a far greater pool of potential study participants than if clinical trials were operating out of one country. This facilitates timely clinical studies of antibiotics, while striving to maintain safety and efficacy standards. Third, the IMI is now engaging with non-European partners such as BARDA's BSA programme. This stands to further mutually improve the clinical capacity of participating initiatives.

BARDA's GSK and AstraZeneca portfolio partnerships are further examples of successful PDPs for antibiotics. These clinical development portfolios allow the BSA and the pharmaceutical companies to quickly determine the viability of a particular project and either add or drop the project from the portfolio, thus minimizing risk and cost. By involving the BSA leadership team in the decision process, BARDA can still ensure that public health priorities are at the forefront of the portfolio development pipeline. This partnership model is also observed in the IMI's ENABLE, a flexible portfolio of projects targeted at early discovery programmes run by SMEs and academic institutions to develop new agents that treat gram-negative bacteria. These more adaptable portfolio models may serve as good examples for future projects in antibiotic R&D.

It worth noting that there are at least 72 research projects with clinical trial aspects that operate at national levels in Europe.[31] These projects likely have minimal coordination, which can be inefficient and risks duplicating work.

5.5.3 Market approval

The EMA and FDA have a number of useful regulatory mechanisms to expedite approval of high-priority antibiotics. Both regulatory agencies have the ability to accelerate the approval process as well as approve antibiotics through adaptive licensing pathways. These regulatory tools indirectly improve NPV of antibiotic projects and can result in timely patient access to new antibiotics. However, these mechanisms highlight that there is a necessary trade-off between flexibility and speed of approval and maintaining high levels of safety and efficacy of authorized antibiotics.

Through TATFAR, the EMA and FDA are working diligently to improve cross-agency collaboration and harmonization of licensing requirements for antibiotics. However, under present regulatory frameworks ensuring that an antibiotic meets both the EMA's and FDA's licensing standards can be time consuming and costly for the developer. Given that both the EMA and FDA have similar goals in terms of antibiotic approval, it may be worth exploring the idea of joint EMA/FDA approval of certain novel antibiotics. Regardless, the present EMA/FDA partnership sets a strong and favourable precedent for future collaboration and harmonization efforts with other national drug regulatory bodies such as the China Food and Drug Administration and Japan's Pharmaceuticals and Medical Devices Agency.

5.5.4 Commercialization

Presently, there are few antibiotic initiatives that target the commercialization aspect of the antibiotic value chain. These include the three end prizes for diagnostic tools and the market exclusivity extensions offered by drug regulatory agencies to qualified antibiotics. Thus, the additional incentives proposed and discussed above (section 5.2.2) tend to fill this gap in the value chain. The IMI's DRIVE-AB programme is also exploring incentive solutions that effect commercialization.

5.6 How are SMEs supported through existing initiatives?

Based on our analysis, it appears that SMEs in particular are lacking support from the existing set of initiatives. As highlighted above, a majority of European public funding is directed to academic institutions for the purposes of basic research. On the clinical end, the IMI's partnerships tend to be with big pharmaceutical companies; ENABLE is an exception (personal communication, Florence Séjourné, CEO of Da Volterra, 2016). There are some notable EU initiatives that specifically target SMEs including InnovFin ID and the EC DG RTD's general funding programmes for SME innovation, which include the SME Instrument, the Fast Track to Innovation scheme and Eurostars. Although not backed by financial incentives, DRIVE-AB has been active in supporting the engagement of SMEs through the BEAM Alliance and advocating for SMEs to be more broadly engaged in IMI2. It is expected that their upcoming recommendations in 2017 will push for greater incentivization of SMEs.

SMEs lack support in the preclinical and early clinical phases of development, which are expensive and necessary for validating access to future venture capital. The InnovFin ID would seem like the perfect mechanism for bridging this barrier, however the InnovFin ID loans require drugs to be already in the clinical phases of development. This substantial requirement may defeat the purpose of having a SME-focused antibiotic R&D initiative.

The InnovFin ID's largest available loan of €75 million may still not be enough to help SMEs through the expensive clinical phases that often exceed €120 million per drug candidate.

It would be prudent to have information on industry preferences for different incentives in order to accurately pinpoint how best to support the different market players. We would expect that SMEs and big pharma have quite different incentive wish lists and both need to be respected.

5.7 Are public health needs reflected in the current set of initiatives?

5.7.1 Stewardship and patient access

According to a 2014 study by Van Boeckel et al., global consumption of antibiotics by humans increased by 36% between 2000 and 2010.[86] Brazil, Russia, India, China and South Africa were responsible for 76% of this increase in consumption despite comprising 40% of the world's population. Overconsumption of antibiotics continues to be a major driver of antibiotic resistance and is a problem faced by both high-income countries and LMICs.[86] Antibiotic stewardship can be facilitated through disease prevention efforts, infection control, surveillance and appropriate prescribing. High-income countries have multiple antibiotic stewardship programmes in place such as systems for monitoring resistance, patient awareness programmes, treatment guidelines for physicians, legislation on antibiotic advertising and restrictions on over-the-counter dispensation. However, in LMICs, antibiotic use is primarily driven by a lack of basic public health measures for controlling infectious disease such as sanitation, clean water and adequate nutrition.[87]

LMICs and even development agencies often do not recognize AMR as a top health priority, despite LMICs suffering the majority of the global health burden from AMR.[88] These countries struggle to attain equitable and affordable access to antibiotics in the first place and thus the overconsumption of antibiotics and subsequent spread of AMR can often be considered secondary problems. It is estimated that 5.7 million people die annually from treatable infectious diseases, most of which are vulnerable to the existing arsenal of antimicrobials.[88,89] More than a million young children die of untreated pneumonia and sepsis annually, almost all of which are in LMICs.[90] In a recent 2016 article in *The Lancet*, Laxminarayan et al. estimate that global provision of antibiotics could mitigate the deaths of 445,000 children under the age of five each year due to community-acquired pneumonia.[87] Thus, antibiotic stewardship cannot be a blunt policy tool that broadly restricts all access to antibiotics in the name of conservation. Ideally, equitable access to antibiotics worldwide will grow alongside restricting inappropriate distribution of antibiotics through regulation and stewardship.[88]

Antibiotic stewardship and patient access are traditionally addressed through public health programmes independent of R&D initiatives. In Europe, these programmes are run by the EC (i.e. DG SANTE) as well as agencies such as the EFSA and ECDC. Thus, few R&D initiatives have explicit stewardship and access policies. This makes more sense given that most initiatives use push mechanisms that are not tied to any post-approval conditions regarding marketing practices or distribution of the antibiotics. However, it is critical that R&D initiatives are interlinked with and reinforce the other aspects of combating AMR. If R&D initiatives debase other AMR programmes then we cannot have an effective global strategy for tackling this complex and evolving threat. In order to address this issue, the DRIVE-AB programme has been tasked with designing and presenting a sustainable new business model for antibiotics that factors in these broader public health priorities. Their final recommendations are expected in 2017.

On 29 February 2016, the WHO held a consultation on the establishment of a global development and stewardship framework to fight AMR. The proposed framework, endorsed by the Global Action Plan on AMR, would "support the development, control, distribution, and appropriate use of new antimicrobial medicines, diagnostic tools, vaccines and other interventions, while preserving existing antimicrobial medicines, and promoting affordable access to existing and new antimicrobial medicines and diagnostic tools, taking into account the needs of all countries."[91] The framework builds on the "policy tripod for addressing antibiotic resistance", which recognizes that resistance needs to be tackled collectively through access, conservation and innovation.[92,93]

5.7.2 Delinkage

It is increasingly recognized that the current patent-based pharmaceutical business model does not sufficiently work for antibiotics. Antibiotic developers are rewarded through market exclusivity, which reinforces the over-marketing and over-consumption of antibiotics that contribute to high levels of resistance.[24] In addition, developers are incentivized to distribute antibiotics based on ability to pay instead of need.[24] Therefore, LMICs often have reduced access to high-value antibiotics.

As a result, delinkage has been proposed by academics, industry representatives and policy makers as the basis for a new business model for antibiotics.[24,94] Delinkage occurs when a drug developer's revenues are separated from the volume of antibiotic sold. In theory, this would be accomplished through a value-based payment to the developer in return for control over the marketing and distribution of the new antibiotic. These payments may be in the form of payer licenses, a full patent buyout, or as AMCs.[30]

Delinkage is a global solution to a global problem, however its practical implementation seems to be its largest barrier to fruition. Delinkage forms that allow firms to retain their intellectual property appear to be more favourably reviewed by industry.[30] Promisingly, a recent declaration was signed by 85 companies and nine industry associations representing global pharmaceutical, diagnostics and biotechnology development in 18 countries, calling on national governments to work with them in developing a new and sustainable antibiotic market.[95] The envisioned antibiotics market would have improved access to all those in need and a reduced incentive to promote antibiotic consumption.

5.7.3 Medical needs

Ensuring that global medical priorities are aligned with those of the developer is critical to producing marketable antibiotics that target high-priority medical needs. The US pipeline analysis (Appendix 1) suggests that there is in fact significant alignment between developer goals and public health needs; gram-negative bacteria and the ESKAPE pathogens are targeted. Moreover, many of the pipeline antibiotics are for the Big Five indications, which are most commonly affected by resistant bacteria.

However, there are multiple antibiotics in the pipeline that target lower priority diseases such as gram-positive acute skin infections. Also, there are very few antibiotics in the development pipeline that offer entirely new mechanisms of action that are not marred by cross-resistance. Low-priority antibiotics in the pipeline suggest that current initiatives do not set out clear objectives in antibiotic R&D.[4] This is one of the problems with push mechanisms; it is challenging to control the direction of private R&D to attain public health priorities. Milestone prizes tied to ongoing target product profiles is one possible method of ensuring push funding is allocated to antibiotic candidates pursuing high-priority medical needs. Larger end prizes linked to target specifications would be an alternative. In a newly published *The Lancet Infectious Diseases* article, Rex and Outterson suggest that a newly marketed antibiotic could receive a base payment end prize plus bonus payments for achieving certain clinical goals.[96] These goals could include having a first-in-class mechanism of action, a clinical spectrum of activity that includes one or more urgent pathogens, have been approved in oral dosage form, or delivered agreed paediatric commitment studies.

Another aspect of this issue pertains to LMICs, which have unique health priorities for infectious disease.[2] Thus, actively seeking involvement from LMICs will be an important step in aligning antibiotic innovation with their medical needs. The EDCTP is a convincing model for accomplishing this as it focuses antibiotic R&D towards LMIC health priorities and actively includes LMIC institutions in the antibiotic R&D process.

The WHO Prequalification of Medicines Programme (PQP) could further support LMIC-focused R&D initiatives like the EDCTP. The PQP is a UN programme managed by the WHO and works in close collaboration with national regulatory agencies and partner organizations to authorize a list of prequalified medicinal products for HIV/AIDS, malaria, TB and reproductive health.[97] The PQP medicine list is used by UN agencies like UNAIDS and UNICEF to guide bulk procurement decisions and ensure that the medicines are used appropriately. The PQP could help steer antibiotic R&D targeting poverty-related infectious diseases, form the basis for a large end prize attached to public procurement (i.e. delinkage) and reinforce the stewardship and access goals of distribution.

6. Conclusions & Recommendations

Spurring global innovation of new antibiotics, alternative therapies and diagnostics tools is integral to effectively combating AMR. However, demand for new antibiotic products far outweighs supply. Only five novel classes of antibiotics have reached the market since 2000. None of these target gram-negative bacteria. This is not surprising given that there are numerous scientific, regulatory and economic barriers that prevent adequate investment in antibiotic R&D.

We have a partial picture of the global antibiotics market. EU and US antibiotic pipeline data shows that are at least 52 antibiotic products in clinical development, the vast majority of which are in Phases I and II. However, this pipeline may only translate into 15 antibiotic products with varying value; less than half would be systemic antibiotics that could target gram-negative bacteria. Only one antibiotic in the development pipeline uses a novel mechanism of action and it is for a limited purpose.

Europe has invested approximately €147 million annually between 2007–13 in antibiotic R&D while the US has invested roughly $260 million (€234 million) in 2015. US investment in antibiotic R&D is expected to grow to $413 million (€380 million) in 2016 after having been constant for five years. However, it is unclear how this difference in EU/US funding has affected outcomes in the antibiotics pipeline. European and US governments appear to have limited means of clawing back these significant contributions and sharing in future profits should their funding result in marketable products.

Our only real insight into private investment in antibiotic R&D is from global data on venture capital funding. Global venture capital in antimicrobial R&D has declined by 28% between the two five year windows of 2004–08 and 2009–13. Venture capital investment in gram-negative antimicrobials has increased by 51% during these two periods, but it still comprises only 12% of total venture capital investment in antimicrobials. The amount of internal capital invested by developers into their own antibiotic projects is unknown.

Numerous initiatives have been implemented to reinvigorate the antibiotic R&D pipeline. In total, we identified 58 active initiatives and sub-initiatives at global, EU and national levels (UK, France, Germany, Netherlands, Sweden, US and Canada) that directly incentivize antibiotic R&D. Also, there are nine initiatives that indirectly support antibiotic R&D by coordinating strategic actions on AMR and seven initiatives that are either proposed or in the introductory stages of implementation.

The antibiotic R&D initiative environment is now crowded. There is room for improvement regarding the coherence and coordination between and within initiatives. Various models of partnership often form the basis for many initiatives, which improves the possibilities for stakeholder collaboration, but can further confuse coordination efforts.

While almost all these initiatives can be seen to be improving antibiotic project NPV, our analysis shows that a far greater number of push incentives are used over pull incentives. This imbalance between push and pull incentives has led to an unequal distribution of initiatives across the antibiotic value chain. The most common incentives of direct project funding, research collaboration, research grants and fellowships for scientific personnel, tend to favour the basic research side of the antibiotic value chain. Thus, SMEs often find that they lack support throughout the challenging preclinical and early clinical phases of development. Surprisingly, taxation policies (a push incentive) were not used to specifically support firms that engage in antibiotic R&D.

In contrast, there are few incentives that support the commercialization end of the value chain such as end prizes, AMCs, and value-based pricing and reimbursement. Moreover, there remains a need for even greater harmonization between the EMA and FDA, as well as other drug regulatory agencies.

Finally, our analysis suggests that antibiotic conservation and patient access objectives are poorly integrated into the existing innovation schemes. Many initiatives have not explicitly linked their incentives to high-priority medical needs in infectious disease.

Given this research report's key findings, we put forth the following sixteen recommendations:

Recommendation 1 Align existing and new antibiotic R&D initiatives to function within the broader One Health approach to AMR.

AMR must be tackled through a unified approach that integrates efforts across human health, veterinary medicine and environmental factors. Antibiotic R&D initiatives must be integrated into a broader AMR agenda that reinforces other aspects of the One Health approach.

Recommendation 2 Consolidate and coordinate existing and new European AMR initiatives and antibiotic R&D initiatives, including clinical trials, under a One Europe approach.

In order to be a leader in the global fight against AMR, Europe must establish coherence and coordination across its own AMR initiatives in a One Europe approach, as initiated by the JPIAMR. This requires alignment of EU policies with member state policies both in terms of tackling AMR and in terms of antibiotic R&D. We encourage the continued organization and networking of antibiotic clinical trials within Europe as well as worldwide.

Recommendation 3 Establish a global AMR policy coordination and governing body that brings worldwide coherence under a One World approach to AMR.

AMR is a global problem that necessitates a global solution. Given the proliferation of AMR and antibiotic R&D initiatives at global, regional and national levels, there needs to be a governing entity that coordinates their activities under a One World approach. A

One World approach would provide a consistent global antibiotic framework to guide all initiatives while respecting the need for diversity and variety in methods to tackling AMR and antibiotic innovation. Multiple international AMR strategies have been proposed; now is the time to turn them into action. The upcoming 2016 UN General Assembly presents an opportunity to engage nations in this One World approach.

Recommendation 4 Intensify efforts to coordinate and expand European and global antibiotic clinical trials programmes under One Europe and One World agendas.

Due to the nature of infectious disease, conducting clinical trials on antibiotics can often be logistically challenging. Significant efficiencies can be gained through clinical trial coordination. There is an opportunity for Europe to build and expand on the solid clinical infrastructure established under the IMI's COMBACTE programme. There are a number of national-level antibiotic clinical trials that could possibly be integrated within the broader EU antibiotic clinical trials network. In addition, expanding collaborative efforts between COMBACTE and BARDA would serve to further strengthen these respective programmes. Finally, the EDCTP offers an excellent model for further expanding European clinical trial efforts beyond EU borders to include more LMICs.

Recommendation 5 Ensure antibiotic incentives are explicitly attached to specific high-priority medical needs in infectious disease.

There is misalignment between the observable antibiotic pipeline and key medical needs in the field of infectious disease. Incentives could be improved by attaching clear target product specifications when possible. Milestone payments can be tied to ongoing target product profiles to ensure that push funding is allocated to antibiotic candidates pursuing high-priority medical needs. Similarly, pull-based end prizes need to outline clear antibiotic characteristics that must be met to qualify for the reward.

Recommendation 6 Ensure that antibiotic incentives reinforce global stewardship and access goals.

Innovation must be balanced with the goals of antibiotic stewardship and affordable access to antibiotics for those in need. The concept of delinkage offers an opportunity to implement a sustainable antibiotic business model that addresses innovation, stewardship and access. Implementation of a delinkage model would require oversight from a new or existing global governing body to administer such a programme.

Recommendation 7 Link push and pull incentive mechanisms in a hybrid approach to stimulating antibiotic R&D.

No single push or pull incentive will provide a comprehensive solution to the failing antibiotic development value chain. Instead, a hybrid approach combining push and pull mechanisms is needed to allow early investment and risk sharing in antibiotic R&D, while also creating credible market commitments and incentives for developers to commercialize novel antibiotics. Major antibiotic R&D initiatives like the IMI, BARDA and InnovFin ID could particularly benefit from applying such hybrid incentive strategies.

Recommendation 8 Launch a global AMR observatory that collects AMR and antibiotic pipeline data, shares knowledge and disseminates best practices in AMR and antibiotic innovation.

Significant gaps exist in our understanding of AMR and the antibiotics market. From an innovation perspective, there is a need to determine the evolving global antibiotic pipeline and the global investments made into the antibiotic pipeline. Ideally, we will be able to learn from this data, share useful knowledge and disseminate best practices as they are developed. Ahead of our recommendation, the WHO is already in the process of designing a global health R&D observatory that could include, as well as extend beyond antibiotics. However, in line with the One Health approach, a global antibiotic R&D observatory would need to be integrated with other aspects of AMR data collection such as disease surveillance.

Recommendation 9 Register European and global commitment to antibiotic pull incentives.

Pull incentives are effective tools for enticing antibiotic developers into the market. However, they require significant monetary commitments to adequately reward developers of authorized high-value antibiotics. Thus, global pooling of resources is required to effectively pull high-value antibiotics into the market. The upcoming United Nations 2016 General Assembly, which will discuss AMR, is an opportunity to pave the way for countries to coordinate and commit to pull incentives.

Recommendation 10 Explore the role for European joint procurement of high-value antibiotics to ensure their conservation.

Joint procurement of antibiotics can provide a method of securing public control of a high-value antibiotic's consumption and distribution across member states. In addition, joint procurement can signal European commitment to purchasing high-value antibiotics at fair prices and can be tailored to reflect differences in countries' ability to pay. The EU is in a unique position to consider developing a joint procurement facility for purchasing high-value antibiotics.

Recommendation 11 Consider the feasibility of European tax policies that encourage antibiotic R&D.

There is a role for coordinated tax incentives in Europe that support firms developing antibiotics and related products. Tax incentives do not require upfront payments by governments and can be tailored to benefit both SMEs and big pharmaceutical companies. Furthermore, tax incentives can leverage tax deferrals as a method of clawing back public investment in antibiotic R&D.

Recommendation 12 Incorporate methods of clawing back public investment in antibiotic R&D into incentive packages.

The public deserves a positive return on their financial investment in antibiotic R&D. Incentives that have clawback arrangements can still support firms throughout development, while also allowing for public purchasers to benefit from their original investment. Clawback policies can supplement both push and pull incentives alike and could take the form of risk-sharing loans, tax deferrals, or AMCs on discounted antibiotics.

Recommendation 13 Improve cooperation and harmonization across global drug regulatory agencies for licensing novel antibiotics.

Poor harmonization in approval requirements between drug agencies can be a significant hurdle for antibiotic developers. Regulatory cooperation must continue between the EMA and FDA, as well as extend beyond TATFAR to include other drug agencies around the world. There may also be merit in examining the role for joint EMA/FDA authorization procedures for novel antibiotics.

Recommendation 14 Address key market weaknesses by further enabling SME participation and facilitating preclinical development.

SMEs continue to be under supported in the antibiotics market despite their contribution to the development pipeline. More initiatives must recognize the specific resource barriers faced by SMEs and ensure that their incentives are accessible and beneficial to SMEs. In particular, SMEs require initial capital support through preclinical and early clinical phases of development, which are often characterized as the R&D 'valley of death'.

Recommendation 15 Explore the incentive preferences of different industry players.

Despite knowing that SMEs and large pharmaceutical companies need to be further incentivized to develop antibiotics, we do not know exactly what types of incentives either type of industry player prefers. Therefore, we recommend exploring industry preferences for different incentives in order to accurately determine how best to support the different market players. This research seems well suited for IMI's DRIVE-AB programme.

Recommendation 16 Investigate the value of different partnership models in antibiotic R&D and learn from the experiences of the BARDA, IMI and JPIAMR.

There is now a wide proliferation of initiatives founded on partnerships. These partnerships vary substantially based on the number and type of organizations involved. There are likely advantages and disadvantages to the different partnership models that can provide insight into positively reforming these initiatives. Therefore, we recommend funding research that investigates the roles of partnerships in antibiotic R&D and learns from the experiences of BARDA, the IMI and the JPIAMR.

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Appendix 1: Antibiotics currently in development or recently approved in the US market

Drug name	Company	Drug class	Expected activity against		Potential indications
			Resistant Gram-neg. ESKAPE pathogens	CDC urgent threat pathogens	HAP = hospital-acquired bacterial pneumonia VAP = ventilator-associated bacterial pneumonia
APPROVED					
Ceftolozane + Tazobactam (Zerbaxa)	Cubist Pharmaceuticals, Inc (wholly owned subsidiary of Merck & Co)	Novel cephalosporin + beta-lactamase inhibitor	Yes	No	Approved 19 December 2014 for complicated urinary tract infections, complicated intra-abdominal infections, acute pyelonephritis (kidney infection); other potential indications: HAP/VAP
Ceftazidime + Avibactam (Avycaz)	Allergan plc (formerly Actavis)/ AstraZeneca plc	Cephalosporin + novel beta-lactamase inhibitor	Yes	Yes	Approved 25 February 2015 for complicated urinary tract infections, complicated intra-abdominal infections, acute pyelonephritis (kidney infection); other potential indications: HAP/VAP, bacteraemia
DEVELOPMENT PHASE 1					
WCK 771	Wockhardt Ltd	Fluoroquinolone	No	No	Bacterial infections
WCK 4873	Wockhardt Ltd	Ketolide (JHR)	No	No	Bacterial infections

Source: data table from the Pew Charitable Trusts.

Appendix 1 (continued): Antibiotics currently in development or recently approved in the US market

Drug name	Company	Drug class	Expected activity against		Potential indications
			Resistant Gram-neg. ESKAPE pathogens	**CDC urgent threat pathogens**	HAP = hospital-acquired bacterial pneumonia VAP = ventilator-associated bacterial pneumonia
WCK 2349	Wockhardt Ltd	Fluoroquinolone (WCK 771 pro-drug)	No	No	Bacterial infections
TD-1607	Theravance Biopharma Inc	Glycopeptide-cephalosporin heterodimer	No	No	Acute bacterial skin and skin structure infections, HAP/VAP, bacteraemia
LCB01-0371	LegoChem Biosciences Inc	Oxazolidinone	No	No	Bacterial infections
OP0595 (RG6080)	Meiji Seika Pharma Co Ltd./Fedora Pharmaceuticals Inc (Roche licensee)	Beta-lactamase inhibitor	Possibly	Possibly	Bacterial infections
BAL30072	Basilea Pharmaceutica Ltd	Monosulfactam	Yes	Yes	Multidrug-resistant Gram-negative bacterial infections
Aztreonam+ Avibactam (ATM-AVI)	AstraZeneca/Allergan (formerly Actavis)	Monobactam + novel beta-lactamase inhibitor	Yes	Yes	Bacterial infections

Appendix 1 (continued): Antibiotics currently in development or recently approved in the US market

Drug name	Company	Drug class	Expected activity against		Potential indications
			Resistant Gram-neg. ESKAPE pathogens	CDC urgent threat pathogens	
MGB-BP-3	MGB Biopharma Ltd		No	Yes	C. difficile infections
CRS3123	Crestone Inc	Methionyl-tRNA synthetase (MetRS) inhibitor	No	Yes	C. difficile infections
DEVELOPMENT PHASE 2					
Zabofloxacin	Dong Wha Pharmaeutical Co Ltd	Fluoroquinolone	No	No	Community-acquired bacterial pneumonia
Radezolid	Melinta Therapeutics Inc	Oxazolidinone	No	No	Acute bacterial skin and skin structure infections, community-acquired bacterial pneumonia
Nemonoxacin[8]	TaiGen Biotechnology Co., Ltd	Quinolone	No	No	Community-acquired bacterial pneumonia, diabetic foot infection, acute bacterial skin and skin structure infections
MRX-I	MicuRx Pharmaceuticals Inc	Oxazolidinone	No	No	Acute bacterial skin and skin structure infections

Appendix 1 (continued): Antibiotics currently in development or recently approved in the US market

Drug name	Company	Drug class	Expected activity against		Potential indications
			Resistant Gram-neg. ESKAPE pathogens	**CDC urgent threat pathogens**	
Gepotidacin (GSK2140944)	GlaxoSmithKline plc	Novel bacterial topoisomerase inhibitor	No	Yes	Respiratory tract infections, acute bacterial skin and skin structure infections, uncomplicated urogenital gonorrhoea
Debio 1452	Debiopharm Group	Fabl inhibitor	No	No	Acute bacterial skin and skin structure infections (staphylococci-specific)
Debio 1450	Debiopharm Group	Fabl inhibitor (Debio 1452 pro-drug)	No	No	Acute bacterial skin and skin structure infections (staphylococci-specific)
CG400549	Crystal Genomics Inc	Fabl inhibitor	No	No	Acute bacterial skin and skin structure infections, osteomyelitis
Brilacidin	Cellceutix Corp.	Defensin-mimetic	No	No	Acute bacterial skin and skin structure infections
Avarofloxacin	Allergan plc (formerly Actavis)	Fluoroquinolone	No	No	Community-acquired bacterial pneumonia, acute bacterial skin and skin structure infections
S-649266	Shionogo Inc	Cephalosporin	Yes	Yes	Complicated urinary tract infections
Ceftaroline + Avibactam	AstraZeneca plc/ Allergan plc (formerly Actavis)	Cephalosporin + novel beta-lactamase inhibitor	Yes	Yes	Bacterial infections

Appendix 1 (continued): Antibiotics currently in development or recently approved in the US market

Drug name	Company	Drug class	Expected activity against		Potential indications
			Resistant Gram-neg. ESKAPE pathogens	CDC urgent threat pathogens	
POL7080	Polyphor Ltd	Macrocycle (protein epitope mimetic) LptD inhibitor	Yes (Pseudomonas)	No	Ventilator-associated bacterial pneumonia (caused by Pseudomonas aeruginosa), lower respiratory tract infection, bronchiectasis
Finafloxacin	MerLion Pharmaceuticals Pte Ltd	Fluoroquinolone	Yes	Possibly	Complicated urinary tract infections, acute pyelonephritis (kidney infection), complicated intra-abdominal infections, acute bacterial skin and skin structure infections
SMT 19969	Summit Therapeutics Inc		No	Yes	C. difficile-associated diarrhoea
Ramoplanin	Nanotherapeutics Inc	Glycolipodepsipeptide	No	Yes	C. difficile relapse prevention
ETX0914	Entasis Therapeutics Inc	Spiropyrimidinetrione DNA gyrase inhibitor	No	Yes	Uncomplicated gonorrhoea
DEVELOPMENT PHASE 2					
Taksta (Fusidic acid)	Cempra Inc.	Fusidane	No	No	Prosthetic joint infections,acute bacterial skin and skin structure infections
Solithromycin	Cempra Inc.	Macrolide (fluoroketolide)	No	Yes	Community-acquired bacterial pneumonia, uncomplicated urogenital gonorrhoea, urethritis

Appendix 1 (continued): Antibiotics currently in development or recently approved in the US market

Drug name	Company	Drug class	Expected activity against		Potential indications
			Resistant Gram-neg. ESKAPE pathogens	CDC urgent threat pathogens	HAP = hospital-acquired bacterial pneumonia VAP = ventilator-associated bacterial pneumonia
Lefamulin (BC-3781)	Nabriva Therapeutics AG	Pleuromutilin	No	No	Acute bacterial skin and skin structure infections, community-acquired bacterial pneumonia, HAP/VAP, osteomyelitis, prosthetic joint infections
Iclaprim	Motif Bio plc	Dihydrofolate reductase (DHFR) inhibitor	No	No	Acute bacterial skin and skin structure infections; HAP
Delafloxacin	Melinta Therapeutics Inc	Fluoroquinolone	Possibly	Possibly	Acute bacterial skin and skin structure infections, HAP, complicated urinary tract infections, complicated intra-abdominal infections
Plazomicin	Achaogen Inc	Aminoglycoside	Yes	Yes	Complicated urinary tract infections, catheter-related blood-stream infections, HAP/VAP, complicated intra-abdominal infections, acute pyelonephritis (kidney infection) (some indications specifically target infections caused by carbapenem-resistant Enterobacteriaceae)
Omadacycline	Paratek Pharmaceuticals Inc	Tetracycline	Yes	Possibly	Community-acquired bacterial pneumonia, acute bacterial skin and skin structure infections, complicated urinary tract infections

Appendix 1 (continued): Antibiotics currently in development or recently approved in the US market

Drug name	Company	Drug class	Expected activity against		Potential indications
			Resistant Gram-neg. ESKAPE pathogens	CDC urgent threat pathogens	HAP = hospital-acquired bacterial pneumonia VAP = ventilator-associated bacterial pneumonia
Imipenem/ cilastatin + relebactam (MK-7655)	Merck & Co Inc	Carbapenem + novel beta-lactamase inhibitor	Yes	Yes	Complicated urinary tract infections, acute pyelonephritis, complicated intra-abdominal infections, HAP/VAP
Eravacycline	Tetraphase Pharmaceuticals Inc	Tetracycline	Yes	Yes	Complicated intra-abdominal infections, complicated urinary tract infections, HAP
Carbavance (RPX7009 + meropenem)	Rempex Pharmaceuticals Inc (wholly owned subsidiary of The Medicines Co)	Meropenem + novel boronic beta-lactamase inhibitor	Yes	Yes	Complicated urinary tract infections, complicated intra-abdominal infections, HAP/VAP, febrile neutropenia, bacteraemia, acute pyelonephritis (some indications specifically target infections caused by carbapenem-resistant Enterobacteriaceae)
Surotomycin	Cubist Pharmaceuticals Inc (wholly owned subsidiary of Merck & Co Inc)	Lipopeptide	No	Yes	C. difficile-associated diarrhoea
Cadazolid	Actelion Pharmaceuticals Ltd	Quinolonyl-oxazolidinone	No	Yes	C. difficile-associated diarrhoea

Appendix 2: BEAM Alliance products in clinical development

Company name	Compound name	Compound category	Product description
DEVELOPMENT PHASE 1			
Alaxia	ALX-009	Bioproduct	Association of 2 endogenous substances with antimicrobial properties compensating the defective innate immune system in cystic fibrosis patients
Ilecra Therapeutics	AAI201	Antibiotic combination	Treatment of suspected or confirmed gram-negative multi drug-resistant infections acquired either in the community or hospital environment
Allecra Therapeutics	AAI202	Antibiotic combination	Treatment of hospital acquired gram-negative multi drug-resistant infections in complicated urinary tract infections (cUTI), complicated intra-abdominal infections (cIAI) and respiratory indications
Arsanis Biosciences	ASN100	Antibody	Combination of two human monoclonal antibodies against S. aureus toxins and expected to be tested both in prophylactic and therapeutic indications
Fab Pharma	FAB001	Small antibiotic molecule	Narrow spectrum antibiotic versus methicillin-resistant S. aereus (MRSA)
MGB BioPharma	MGB-BP-3	Small antibiotic molecule (novel antibacterial)	Novel, oral antibiotic potential for superiority over current C. difficile standard therapy
SETUBIO	Phytogynal	Bioproduct	Plant bioproduct enhancing the microbiote to stimulate the immune system and fight against pathogens settlement
SETUBIO	Titroléane	Bioproduct	Large spectrum bioproduct efficient on antibiotic resistant clinical strains
Technophage	TP-102	Bacteriophage	Combination of phages targeting Staphylococcus, Pseudomonas and Acinetobacter species for treatment of infected chronic ulcers, particularly diabetic foot ulcers

Source: BEAM Alliance Position Paper.

Appendix 2 (continued): BEAM Alliance products in clinical development

Company name	Compound name	Compound category	Product description
DEVELOPMENT PHASE 1/2			
AntibioTx	ATx2.1	Small antibiotic molecule	Topical antibiotic versus S. aureus, S. pyogenes, P. acnes and resistant strains, for treatment of bacterial skin infections
Pherecydes Pharma	PP0121	Bacteriophage	Mix of 13 lytic phages targeting E. coli for burn wound infections
Pherecydes Pharma	PP1131	Bacteriophage	Mix of 12 lytic phages targeting P. aeruginosa for burn wound infections
DEVELOPMENT PHASE 2			
Da Volterra	DAV132	Medical device	Oral therapy protecting intestinal micro-biota from antibiotic-induced damage, including prevention of C. difficile infections
Destiny Pharma	XF-73	Small antibiotic molecule (novel antibacterial)	Anti-staphylococcal drug, addressing antibiotic resistance, nasal gel for prevention of infection in at-risk patients
Helperby Therapeutics	ARB 1-6	Antibiotic combination	Helperby Pipeline combinations for cUTIs (inc. CREs), cystic fibrosis, nasal MRSA, gingivitis, halitosis, skin infections
Morphochem/ Biovertis	MCB3837/ MCB3681	Small molecule antibacterial	Intravenous narrow spectrum Gram-positive antibacterial for the treatment of C. difficile infections
NAICONS	CB-06-01	Small antibiotic molecule (novel antibacterial)	New chemical class antibiotic highly selective against P. acnes developed in collaboration with Cassiopea SpA
NovaBiotics Ltd	Lynovex	Adjuvant therapeutic	Aminothiol – small molecule initially intended for use in treating respiratory infections associated with cystic fibrosis
Polyphor	POL7080	Macrocyclic antibiotic	Pseudomonas selective, protein epitope mimetic targeting LptD protein essential for outer membrane biosynthesis. Potential indications include VAP, non-cystic fibrosis bronchiectasis and cystic fibrosis
DEVELOPMENT PHASE 3			
Immunosystem AB	Anti-Pseudomonas IgY	Antibody	Prevention of lung infections caused by P. aeruginosa in cystic fibrosis patients

Appendix 3: Overview of initiatives supporting antibiotic R&D

Initiative	Description	AB R&D incentives	Value chain targeted	Timeframe	AB R&D funding
International initiatives supporting antibiotic R&D					
Joint Programming Initiative on Antimicrobial Resistance	JPIAMR coordinates national funding from 22 countries and supports collaborative action to fill existing knowledge gaps in AMR. Developed strategic research agenda that provides a framework for future investment in research priorities.	- Collaborative networking See below for others	- Basic research - Preclinical development	2011–ongoing	Yes – see below
• 1st Joint Call InnovaResistance: Innovative approaches to address antibacterial resistance	Prevention of infection, treatment development, target identification for antibacterial drug development, and pharmacokinetics; call promoted by 14 funding agencies in 12 countries with 7 projects selected	- Direct project funding - Research collaborations	- Basic research	2015–2017	€8.1 million
• 2nd Joint Call	Repurposing of neglected antibiotics, characterizing antibiotics and antibiotic/non-antibiotic combinations; call promoted by 10 funding agencies in 9 countries with 3 projects selected	- Direct project funding - Research collaborations - PDP	- Basic research - Preclinical development	2016–2018	€4.5 million
• 3rd Joint Call JPI-EC-AMR co-funded Call	Dynamics of transmission and selection of AMR at genetic, bacterial, animal, human, societal and environmental levels, to design and evaluate preventative and intervening measures for controlling resistance; call promoted by 22 funding agencies in 19 countries and the EC	- Direct project funding - Research collaborations - PDP - Sharing R&D resources	- Basic research - Preclinical development	Open	€30 million available for funding projects

= initiatives and institutions that provide direct push or outcome-based pull incentives for antibiotic R&D. = drug agencies or regulators that invoke lego-regulatory pull incentives for antibiotic R&D. = initiatives and institutions that only indirectly support antibiotic R&D by coordinating strategic actions on AMR (e.g. meetings, strategies, action plans, policy and economic research etc.). = initiatives and institutions that have been proposed or have not been fully implemented.

Appendix 3 (continued): Overview of initiatives supporting antibiotic R&D

Initiative	Description	AB R&D incentives	Value chain targeted	Timeframe	AB R&D funding
International initiatives supporting antibiotic R&D (continued)					
• 4th Joint Call	The 4th call is a rapid action call for leading scientists in the field to establish international research networks and develop guidelines and/or best practice frameworks; suggested topics include: guidelines on antibiotic use, affordable stewardship, surveillance in primary care, new anti-infectives, clinical trial design, rapid diagnostic tests and role of environmental factors	- Direct project funding - Research collaborations - Collaborative network	TBD	Call period: April–June 2016	Up to €50,000 for each working group
European and Developing Countries Clinical Trials Partnership	EDCTP funds collaborative research that accelerates clinical development of new or improved treatments for key poverty-related infectious diseases; many studies focus on AMR. The second generation of the programme, EDCTP2, is now being implemented with 14 EU countries and 14 African countries participating; budget: €1.36 billion with EC contributing up to €683 million over 10 years if matched by member EU countries	- Research grants and fellowships for scientific personnel - Direct project funding - Research collaborations - Investment in R&D capacity - Sharing R&D resources - PDP	- Clinical development	EDCTP: 2003–2013 EDCTP-2: 2014–2024	~€93 million for drug R&D projects (2003–2014)
Transatlantic Taskforce on Antimicrobial Resistance	TATFAR is a cooperative programme between the US and EU in three key areas required for tackling AMR: 1. Appropriate therapeutic use of antimicrobial drugs in medical and veterinary settings 2. Prevention of healthcare and community-associated drug-resistant infections 3. Strategies for improving the pipeline of new antimicrobial drugs	- International harmonization - Collaborative network - Priority setting	- Basic research - Preclinical development - Clinical development - Market authorization - Commercialization	2009 – ongoing	None

Appendix 3 (continued): Overview of initiatives supporting antibiotic R&D

Initiative	Description	AB R&D incentives	Value chain targeted	Timeframe	AB R&D funding
International initiatives supporting antibiotic R&D (continued)					
Global Action Plan on Antimicrobial Resistance	GUARD is a global call to action among all WHO member states, the UN Secretariat, international organizations and other partners to ensure the continuity of the ability to treat and prevent and prevent infectious diseases with effective and safe medicines. One critical strategic objective is to develop the economic case for sustainable investment that takes into account the needs of all countries, and increases investment in new medicines, diagnostic tools, vaccines and other interventions	- Priority setting - Collaborative network	- Basic research - Preclinical development - Clinical development - Market authorization - Commercialization	2015 – ongoing	None
Global Union for Antibiotics Research and Development Initiative	Arising from the 2015 Berlin Conference of G7 Health Ministries, GUARD is an agreement among G7 nations that a joint approach among countries is required to effectively fight AMR. An important aspect of GUARD is the joint recognition that continued efforts are needed to stimulate the antibiotic R&D pipeline	- Collaborative network	- Basic research - Preclinical development - Clinical development - Market authorization - Commercialization	9 October 2015	None
Global Antibiotic Research and Development Facility	A proposed joint venture between the WHO and the DNDi to support all aspects of the antibiotic R&D pipeline; a primary goal will be to develop new antibiotic treatments addressing AMR while ensuring suitability and accessibility of new tools for resource limited settings; the partnership will work closely with all stakeholders from countries of all income levels	TBD	- Basic research - Preclinical development - Clinical development - Market authorization - Commercialization	TBD	TBD

Appendix 3 (continued): Overview of initiatives supporting antibiotic R&D

Initiative	Description	AB R&D incentives	Value chain targeted	Timeframe	AB R&D funding
EU initiatives supporting antibiotic R&D					
Directorate General for Research and Innovation, European Commission	The DG RTD defines and implements policies that support a research and innovation friendly environment for the purpose of creating needed products and services as well as economic growth and jobs	- Direct project funding - Sharing R&D resources - Research grants and fellowships for scientific personnel - Collaborative networking - Research collaborations - Financial debt instruments	- Basic research - Preclinical development - Clinical development	Ongoing	Exact figure unknown (see below for some initiatives)
Innovative Medicines Initiative New Drugs for Bad Bugs Program	ND4BB is a programme under IMI, a public-private partnership between the EU and the EFPIA. It addresses key challenges from early discovery to development of new medicines against AMR and facilitates collaboration among stakeholders, e.g. big pharma, SMEs, academic, governmental and non-governmental organizations	See below:	- Basic research - Preclinical development - Clinical development - Market authorization - Commercialization	2013–2021	ND4BB: €606 million FP7 contribution: €312 million
• TRANSLOCATION	Research collaboration aimed at understanding how to get antibiotics permanently into multi-drug resistant gram-negative bacteria; 27 public and private partners across 9 countries	- Public-private research collaborations - Direct project funding - Sharing R&D resources - Investment in R&D capacity	- Basic research	2013–2017	Total: €29 million FP7 contribution: €15 million

Appendix 3 (continued): Overview of initiatives supporting antibiotic R&D

Initiative	Description	AB R&D incentives	Value chain targeted	Timeframe	AB R&D funding
EU initiatives supporting antibiotic R&D (continued)					
• ENABLE European Gram-Negative Antibacterial Engine	Discovery platform with an innovative governance model that supports pre-clinical and early clinical research into antibiotics that target gram-negative bacteria; designed to fund only most promising programmes at any given time; 32 public and private partners across 13 countries	- PDP - Direct project funding - Sharing R&D resources - Investment in R&D capacity	- Basic research - Preclinical development - Clinical development	2014–2020	Total: €101 million FP7 contribution: €59 million
• COMBACTE Combatting Bacterial Resistance in Europe	R&D support project that facilitates clinical trials with new antibiotics; involves setting up a sustainable high-quality pan-European clinical research network of investigators/clinical sites (CLIN-Net) and laboratory surveillance network (LAB-Net); improved clinical trial design/methodology conducting clinical trials with innovative anti-infectious agents developed by the pharmaceutical companies participating in the project; 31 public and private partners across 13 countries	- PDP - Direct project funding - Sharing R&D resources - Investment in R&D capacity	- Clinical development	2013–2019	Total: €250 million FP7 contribution: €109 million
• COMBACTE-CARE COMBACTE – Carbapenem Resistance	R&D support project that focuses on how to rapidly detect and treat Carbapenem-resistant enterobacteriaceae. Builds on CLIN-Net and LAB-Net; clinical trials of a novel antibiotic combination product; 21 public and private partners across 10 countries	- PDP - Direct project funding - Sharing R&D resources - Investment in R&D capacity	- Clinical development	2015–2020	Total: €86 million FP7 contribution: €24 million

Appendix 3 (continued): Overview of initiatives supporting antibiotic R&D

Initiative	Description	AB R&D incentives	Value chain targeted	Timeframe	AB R&D funding
EU initiatives supporting antibiotic R&D (continued)					
• COMBACTE-MAGNET COMBACTE – Molecules Against Gram-Negative Infections	R&D support project that will evaluate new approaches to preventing P. aeruginosa infection, particularly in pulmonary infections in ICU patients, and treating patients with MDR infections; builds on CLIN-Net and LAB-Net and will establish new epidemiological network EPI-Net; clinical trials with innovative anti-infectious agents developed by the pharmaceutical companies participating in the project. 38 public and private partners across 9 countries	- PDP - Direct project funding - Sharing R&D resources - Investment in R&D capacity	- Basic research - Preclinical development - Clinical development	2015–2021	Total: €169 million FP7 contribution: €75 million
• iABC Inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis	R&D support project of two inhaled antibiotics for treating respiratory infection in patients with bronchiectasis or cystic fibrosis; 28 public and private partners across 9 countries	- PDP - Sharing R&D resources - Investment in R&D capacity	- Preclinical development - Clinical development	2015–2020	Total: €51 million FP7 contribution: €24 million
• DRIVE-AB	Collaborative research project aimed at generating and testing alternative economic strategies and reward models that incentivize R&D of new antibiotics, while ensuring antibiotic stewardship and patient access; 23 public and private partners across 11 countries	- Development of new economic model for antibiotic R&D	- Basic research - Preclinical development - Clinical development - Market authorization - Commercialization	2014–2017	Total: €11 million FP7 contribution: €6million

Appendix 3 (continued): Overview of initiatives supporting antibiotic R&D

Initiative	Description	AB R&D incentives	Value chain targeted	Timeframe	AB R&D funding
EU initiatives supporting antibiotic R&D (continued)					
• IMI – RAPP-ID	Collaborative research project facilitating the development of rapid, point-of-care test platforms for infectious diseases; 18 public and private partners across 7 countries	- PDP - Direct project funding - Sharing R&D resources	- Basic research - Preclinical development - Clinical development - Market authorization - Commercialization	2011–2016	Total: €14 million FP7 contribution: €7million
• IMI – PreDiCT-TB	Model-based preclinical development of anti-TB drug combinations that can target drug-resistant strains of the disease;19 public and private partners across 8 countries	- PDP - Direct project funding - Sharing R&D resources	- Basic research - Preclinical development - Clinical development	2012–2017	Total: €29 million FP7 contribution: €15million
• Better use of Antibiotics Prize	Monetary prize awarded for developing a rapid test to identify, at the point of care, patients with upper respiratory tract infections that can be treated safely without antibiotics	- End prize	- Commercialization	2015–2016	€1 million
Innovative Medicines Initiative 2	Second iteration of the IMI, which will be funded by Horizon 2020; AMR is a key topic on its strategic research agenda; additional projects under the ND4BB programme are expected; total budget: €3.3 billion (€1.64 billion from FP8)	TBD	TBD	2014–2024	TBD

Appendix 3 (continued): Overview of initiatives supporting antibiotic R&D

Initiative	Description	AB R&D incentives	Value chain targeted	Timeframe	AB R&D funding
EU initiatives supporting antibiotic R&D (continued)					
InnovFin Infectious Disease Finance Facility	Risk-sharing loan schemes offered to EU organizations developing vaccines, drugs, medical and diagnostic devices, and research infrastructures for combating infectious diseases; targets projects passed the pre-clinical stage and seeking clinical validation	- Financial debt instruments	- Clinical development	2014–2020	Loan size: €7.5–75 million
European Medicines Agency	European drug agency responsible for the market authorization of antibiotics submitted through their centralized procedure on behalf of member states; offers a number of accommodations to developers of antibiotics; key member of TATFAR; responsible for providing guidance to developers on market authorization of both human and veterinary medicines	- Accelerated assessment - Free protocol assistance and cheaper scientific advice for SMEs - Adaptive licensing - Market exclusivity extensions	- Market approval - Commercialization	ongoing	None

Appendix 3 (continued): Overview of initiatives supporting antibiotic R&D

Initiative	Description	AB R&D incentives	Value chain targeted	Timeframe	AB R&D funding
US initiatives supporting antibiotic R&D					
National Institute for Allergy and Infectious Diseases, National Institutes for Health NIAID conducts and supports basic and applied research to better understand, treat and prevent infectious, immunologic and allergic disease. NIH budget: US $30.3 billion (FY14); NIAID budget: US $4.4 billion (FY14)		- Direct project funding - Sharing R&D resources - Research grants and fellowships for scientific personnel - Investment in R&D capacity - Collaborative network	- Basic research - Preclinical development - Clinical development	Ongoing	Unknown
• Antimicrobial Resistance Rapid, Point-of-Care Diagnostic Test Challenge	Prize competition sponsored by the NIH and BARDA for the delivery of a rapid point-of-care diagnostic tool that can be used to identify bacterial infections	- Prize competition	- Commercialization	2015	Prize of up to $20 million
• Antibacterial Resistance Leadership Group	Led by Duke Medicine, ALRG develops, designs, implements, and manages a clinical research agenda to increase knowledge of antibacterial resistance; aims to advance research by building transformational trials	- Direct project funding - Public-private research collaborations - Sharing R&D resources	- Basic research	2013–ongoing	US $62 million grant from NIAID over 6.5 years
Biomedical Advanced Research and Development Authority Programme operating within the US Department of Health and Human Services that provides an integrated, systematic approach to the development and purchase of necessary vaccines, drugs, therapies, and diagnostic tools for public health emergencies; largely funded through the Project BioShield Act		- AMC See below for others	- Preclinical development - Clinical development - Commercialization	2006–ongoing	

Appendix 3 (continued): Overview of initiatives supporting antibiotic R&D

Initiative	Description	AB R&D incentives	Value chain targeted	Timeframe	AB R&D funding
US initiatives supporting antibiotic R&D (continued)					
• Broad Spectrum Antimicrobials Program	Programme within BARDA focused on tackling AMR; currently supporting development of six prospective antibiotics	- PDP - Direct project funding	- Preclinical development - Clinical development	2010–ongoing	FY15: $79 million FY16: $182 million
• BARDA/GSK Partnership	Partnership agreement between BARDA and GlaxoSmithKline to develop a portfolio of drug candidates with dual uses in treating illnesses caused by bioterrorism agents and antibiotic-resistant infections	- Public-private research collaboration - PDP	- Preclinical development - Clinical development	2013–2018	Up to $200 million ($40 million initially)
• BARDA/AstraZeneca Partnership	Partnership agreement between BARDA and AstraZeneca to develop a portfolio of drug candidates with dual uses in treating illnesses caused by bioterrorism agents and antibiotic-resistant infections	- Public-private research collaboration - PDP	- Preclinical development - Clinical development	2015–2020	Up to $170 million ($50 million initially)

Appendix 3 (continued): Overview of initiatives supporting antibiotic R&D

Initiative	Description	AB R&D incentives	Value chain targeted	Timeframe	AB R&D funding
US initiatives supporting antibiotic R&D (continued)					
US Food and Drug Administration	Drug agency responsible for the market authorization of antibiotics in the US; offers a number of accommodations to developers of antibiotics	- Fast track designation - Priority review designation - QIDP designation (fast track, priority review, market exclusivity extension) (GAIN Act) - Breakthrough therapy designation - LPAD designation (proposed – 21st Century Cures Act) - Market exclusivity extensions	- Market approval - Commercialization	Ongoing	None
GAIN Act	Ratified in 2012, the GAIN Act provides a number of regulatory and legal incentives for the development of drugs intended to treat “qualified infectious diseases”	- 5 years of additional market exclusivity - Priority review and fast track approval - FDA guidance for antibiotic development	- Market approval - Commercialization	2012–ongoing	None
Pew Charitable Trusts	Pew is a large independent charity that has dedicated resources to tackling AMR; their Antibiotic Research Project has three priorities: removing the regulatory, scientific and economic barriers to antibiotic innovation, establishing antibiotic stewardship programmes and ending antibiotic overuse in veterinary settings	- Research collaborations	- Basic research - Preclinical development - Clinical development	Ongoing	None

Appendix 3 (continued): Overview of initiatives supporting antibiotic R&D

Initiative	Description	AB R&D incentives	Value chain targeted	Timeframe	AB R&D funding
US initiatives supporting antibiotic R&D (continued)					
Clinical Trials Transformation Initiative – Antibacterial Drug Development	PPP to identify and promote practices to increase the quality and efficiency of clinical trials for antibacterial development by generating empirical data on how trials are currently conducted, leading to recommendations for improvement	- Public-private research collaborations	- Clinical development - Market approval	2007–ongoing	None
Foundation for National Institutes for Health – Biomarkers Consortium	PPP for biomedical research to discover, develop and seek regulatory approval for biological markers to support new drug development, preventative medicine and medical diagnostics; number of active projects on clinical trials for antibacterial drugs (HABP, VABP, ABSSSI, CABP)	- Public-private research collaborations	- Clinical development - Market approval	2006–ongoing	Unknown
Infectious Disease Society of America 10x'20 Initiative	NGO advocacy initiative that seeks a global commitment to create an antibiotic R&D enterprise powerful enough to produce 10 new systemic antibiotics by 2020	- PPP for legislative, regulatory and funding solutions to antibiotic R&D	- All	2010–ongoing	None
21st Century Cures Act Proposed US bill aimed at speeding up the approval of certain high demand drugs and devices. Proposed NIH budget increase: 3% annually, three years (~$1.5 billion)		- LPAD-like approval for QIDPs - Collaborative research See below	- Basic research - Market approval - Commercialization	Proposed	Unknown

Appendix 3 (continued): Overview of initiatives supporting antibiotic R&D

Initiative	Description	AB R&D incentives	Value chain targeted	Timeframe	AB R&D funding
US initiatives supporting antibiotic R&D (continued)					
• NIH Innovation Fund	Part of the 21st Century Cures Act, the Fund aims to incentivize biomedical R&D in three areas: precision medicine, young investigators and "other". The details of the fund have yet to be delineated through the legislative process; $2 billion annually, five years ($10 billion)	- End prize - Direct project funding	- Basic research - Commercialization	Proposed	Unknown
Developing an Innovative Strategy for Antimicrobial Resistance Act	Proposed bill that would create a new regulatory designation status – DISARM status – which would increase federal reimbursement for certain antibiotics	- Reimbursement	- Commercialization	Proposed	Unknown
Canadian initiatives supporting antibiotic R&D					
Institute of Infection and Immunity, Canadian Institutes of Health Research CIHR-III supports research and helps to build capacity in the areas of infectious disease and the body's immune system; AMR is a primary strategic objective of the CIHR-III; primarily supporting investment in AMR surveillance and antibiotic stewardship; 2010–2015 AMR funding: C$96.1 million; JPIAMR funding contribution to date: C$7.6 million		- Research grants and fellowships for scientific personnel - Direct project funding	- Basic research	Ongoing	Unknown
• Novel Alternatives to Antibiotics Funding Opportunity	Augments existing CIHR funding opportunities by attracting applications focused on novel approaches to antibiotic resistance; combines input from 26 different partners spanning government, pharma industry, agricultural industry, academia and NGOs	- Public-private research collaborations - Research grants and fellowships for scientific personnel - Direct R&D funding	- Basic research	200 –2013	C$13 million

Appendix 3 (continued): Overview of initiatives supporting antibiotic R&D

Initiative	Description	AB R&D incentives	Value chain targeted	Timeframe	AB R&D funding
Canadian initiatives supporting antibiotic R&D (continued)					
• Canada-UK Partnership on Antibiotic Resistance	Partnership between the UK MRC and CIHR that built on existing collaborations between the two countries; focus on basic research for identifying antibiotic candidates and building research capacity	- Direct R&D funding - Collaborative networking	- Basic research	2009–2015	Total: C$8 million CIHR: C$4 million
Canadian Foundation for Infectious Diseases	Charitable foundation that supports research, education and advocacy missions of projects tackling issues of infectious disease	- Research grants and fellowships for scientific personnel	- Basic research	Ongoing	Unknown
Canadian Society of Microbiologists	Fosters advancement and collaboration in the field of microbiology, with antibiotic research being one key focus area	- Research grants and fellowships for scientific personnel	- Basic research	Ongoing	Unknown
UK initiatives supporting antibiotic R&D					
Medical Research Council	Public research organization that funds research across the biomedical spectrum in all major disease areas; total budget: £771 million (2014/2015)	- Research grants and fellowships for scientific personnel - Public-private research collaborations - Direct project funding - Collaborative networking	- Basic research - Preclinical development - Clinical development	Ongoing	Unknown
• Antimicrobial Resistance Funders' Forum	Forum established for sharing information on activities related to AMR by member organizations such as the research councils, health departments, government bodies, and charities	- Direct project funding - Sharing R&D resources	- Basic research - Preclinical development - Clinical development		Unknown

Appendix 3 (continued): Overview of initiatives supporting antibiotic R&D

Initiative	Description	AB R&D incentives	Value chain targeted	Timeframe	AB R&D funding
UK initiatives supporting antibiotic R&D (continued)					
• UK Clinical Research Collaboration/ Translational Infections Research Initiative	Partnership of funders (NIH, MRC, Wellcome Trust, and others) to carry out research relevant to AMR and infection control	- Research grants and fellowships for scientific personnel - Public-private research collaboration	- Basic research - Preclinical development - Clinical development	2008–2015	£16.5 million
• Tackling AMR – A Cross Council Initiative	Interdisciplinary collaboration initiative focused on four themes to support antibiotic research, encompassing academia, biopharma, diagnostic companies, veterinary and the health service; currently funding Theme 1 (Understand resistant bacteria); funded through the AMRFF	- PDP - Public-private research collaboration - Research grants and fellowships for scientific personnel - Sharing R&D resources	- Basic research - Preclinical development - Clinical development	2014–ongoing	Unknown
• UK-China AMR Partnership Initiative	Cross-border collaborative initiative between several UK research councils and the National Science Foundation of China that will fund research on the clinical and veterinary challenges of AMR in China; £4.5 million contributed by UK and ¥3 million contributed by China	- Direct project funding - Research collaborations - Sharing R&D resources - Investment in R&D capacity - Collaborative networking	- Basic research - Preclinical development - Clinical development	2016–ongoing	Unknown

Appendix 3 (continued): Overview of initiatives supporting antibiotic R&D

Initiative	Description	AB R&D incentives	Value chain targeted	Timeframe	AB R&D funding
UK initiatives supporting antibiotic R&D (continued)					
• UK-India AMR research centres	Cross-border collaborative project between the MRC and the Government of India's Department of Biotechnology to establish two AMR research centres: The Cambridge-Chennai Centre Partnership on Antimicrobial Resistant TB and The UK-India Centre for Advanced Technology for Minimizing the Indiscriminate Use of Antibiotics; ~£6 million jointly contributed by UK and India	- Direct project funding - Research collaborations - Sharing R&D resources - Investment in R&D capacity - Collaborative networking	- Basic research - Preclinical development - Clinical development	2015–ongoing	Unknown
Longitude Prize	Monetary prize awarded for creating a cost-effective, accurate, rapid and easy-to-use test for bacterial infections	- End prize	- Basic research - Preclinical development - Clinical development	2014–2019	£10 million
Wellcome Trust	Independent global charity that has provided significant funding and support for research tackling AMR; funds and supports AMR Review and Fleming Fund, among other projects; contributed over £200 million in the last 10 years to AMR-related projects	- Direct project funding - Sharing R&D resources	- Basic research - Preclinical development - Clinical development	Ongoing	Unknown
Antibiotic Research UK	National charity dedicated to finding new antibiotics against resistant bacteria; provides funding for basic research with the goal of developing three antibiotic resistance breakers and two new classes of antibiotic	- Direct project funding	- Basic research	2014–ongoing	£220K as of October 2015

Appendix 3 (continued): Overview of initiatives supporting antibiotic R&D

Initiative	Description	AB R&D incentives	Value chain targeted	Timeframe	AB R&D funding
UK initiatives supporting antibiotic R&D (continued)					
British Society of Antimicrobial Chemotherapy	UK-based inter-professional organization that has provided research support and funding in antibiotic innovation, among other important aspects of combating AMR; offer 1 year project grants of £15,000 and one year research grants of £50,000	- Research grants and fellowships for scientific personnel	- Basic research	2071–ongoing	Unknown
Biomedical Catalyst	A joint Innovate UK and MRC programme with funding for innovative SMEs and researchers looking to work either individually or in collaboration to develop solutions to healthcare challenges	- Research grants and fellowships for scientific personnel	- Basic research - Preclinical development - Clinical development - Commercialization	2011–ongoing	Unknown
O'Neill Review on Antimicrobial Resistance	Review exploring global solutions to AMR; published numerous reports with recommendations for tackling AMR and improving the scientific, regulatory, and market environments for antibiotic innovation; final report with recommendations due in 2016	- Collaboration among key stakeholders to determine R&D pipeline lever solutions	- All	2014–2016	Request: AMR Innovation Fund: USD $2 billion over five years

Appendix 3 (continued): Overview of initiatives supporting antibiotic R&D

Initiative	Description	AB R&D incentives	Value chain targeted	Timeframe	AB R&D funding
UK initiatives supporting antibiotic R&D (continued)					
Fleming Fund	In response to O'Neill Review recommendations, the Fleming Fund will establish overseas development aid to build laboratory capacity and surveillance networks in developing countries to address the issues of AMR and infectious disease; UK government will work with Wellcome Trust, Bill and Melinda Gates Foundation, Institut Pasteur International Network and other partners to launch the fund	TBD	TBD	2016–2021	£195 million
French initiatives supporting antibiotic R&D					
The French National Research Agency	ANR provides funding for project-based research in all fields of science, including AMR	- Public-private research collaborations - Direct project funding	- Basic research	2005–ongoing	Unknown
The French National Institute of Health and Medical Research French national agency offering strategic, scientific and operational coordination of biomedical research		- Public-private research collaborations - Direct project funding - Research grants and fellowships for scientific personnel	- Basic research - Preclinical development - Clinical development	2009–ongoing	Unknown
• Inserm (Transfert)	Incorporated subsidiary of Inserm focusing on adding value and minimizing risk for innovative projects at pre-commercial stages; supports researchers establish proof of concept, registering patents and searching for industrial partners	- Public-private research collaborations - Sharing R&D resources	- Preclinical development	Unknown	Unknown

Appendix 3 (continued): Overview of initiatives supporting antibiotic R&D

Initiative	Description	AB R&D incentives	Value chain targeted	Timeframe	AB R&D funding
French initiatives supporting antibiotic R&D (continued)					
• French National Alliance for Life Sciences and Health	AVIESAN is a collection of key academic stakeholders in the country representing research institutes, universities, and hospitals; organized into ten thematic multi-organization institutes including one dedicated to immunology, inflammation, infectiology, and microbiology	- Research grants and fellowships for scientific personnel	- Basic research	Unknown	Unknown
German initiatives supporting antibiotic R&D					
German Federal Ministry of Education and Research National governmental body supporting innovative projects and ideas in research through targeted funding programmes		See below	- Basic research - Preclinical development	Unknown	Unknown
• German Centre for Infection Research	Alliance of universities, university hospitals and federal research institutions with expertise in the area of infectious diseases; aim is to accelerate the transmission of research results into practice; two out of nine Thematic Translational Units devote their research to AMR	- Direct project funding - Research collaborations	- Preclinical development	Unknown	Unknown
• InfectControl 2020	Facilitates cooperation between scientists and industry in collaboration with patient associations and the general public; aims to develop new strategies for early recognition, containment and combating of infectious diseases	- Research collaborations - Research grants and fellowships for scientific personnel	- Basic research - Preclinical development	2014–ongoing	Unknown

Appendix 3 (continued): Overview of initiatives supporting antibiotic R&D

Initiative	Description	AB R&D incentives	Value chain targeted	Timeframe	AB R&D funding
German initiatives supporting antibiotic R&D (continued)					
German Research Foundation	German research agency currently supporting a number of basic research projects on the subject of antibiotics within the field of AMR	- Direct project funding - Research collaborations	- Basic research	Unknown	Unknown
Leibniz Institute for Natural Product Research and Infection Biology	PPP model with a goal to promote research in new therapies for infectious diseases and the search for new substances for antibiotics	- Public-private research collaborations	- Basic research - Preclinical development	Unknown	Unknown
Dutch initiatives supporting antibiotic R&D					
Netherlands Center for One Health	Forms the basis for a high-quality consortium with top expertise in the field of AMR; research agenda promotes multidisciplinary, translational research, spanning the entire spectrum from fundamental research to clinical studies on patients	- Research collaborations	- Basic research - Preclinical development - Clinical development	Unknown	Unknown
Netherlands Organisation for Health Research and Development National governmental body that promotes quality and innovation in the field of health research and health care, initiating and fostering new developments		- Direct project funding	- Basic research - Preclinical development	Unknown	Unknown
• Priority Medicines Antimicrobial Resistance Programme	Dutch research programme conducting basic and applied research in the field of AMR	- Direct project funding	- Basic research - Preclinical development	2009–2018	€14.76 million

Appendix 3 (continued): Overview of initiatives supporting antibiotic R&D

Initiative	Description	AB R&D incentives	Value chain targeted	Timeframe	AB R&D funding
Swedish initiatives supporting antibiotic R&D					
Swedish Research Council	Swedish government agency that provides funding for basic research in all research domains; AMR is a key priority for the SRC.	- Research grants and fellowships for scientific personnel - Research collaborations	- Basic research	Ongoing	Unknown
Vinnova	Government agency that funds needs-driven innovation in priority areas, including AMR	- Research grants and fellowships for scientific personnel - Research collaborations	- Basic research - Preclinical development - Clinical development	Ongoing	Unknown
Formas	Government agency funding basic research in agriculture, veterinary sciences and environmental research domains; AMR is a key priority	- Research grants and fellowships for scientific personnel - Research collaborations	- Basic research	Ongoing	Unknown

Appendix 4: Criteria-based analysis of initiatives supporting antibiotic R&D

Initiative	Improves NPV?	Enables participation of SMEs?	Encourages participation of large cap firms?	Facilitates cooperation and synergy?	Promotes antibiotic conservation and patient access?	Targets specific high-priority medical needs?
International initiatives supporting antibiotic R&D						
JPIAMR	✔	✖	✖	✔	✔	✔
• 1st Joint Call	✔	✖	✖	✔	✖	✔
• 2nd Joint Call	✔	✖	✖	✔	✖	✔
• 3rd Joint Call	✔	✖	✖	✔	✖	✔
EDCTP	✔	✔	✔	✔	✔	✔
EC: DG RTD	✔	✔	✔	✔	✖	✔
• IMI: ND4BB	✔	✖	✔	✔	✖	✔
• ND4BB: TRANSLOCATION	✔	✖	✔	✔	✖	✔
• ND4BB: ENABLE	✔	✔	✔	✔	✖	✔

Note: A question mark indicates that it is unclear whether a particular criterion is fulfilled or not. Initiatives that did not use direct incentives or have not been fully implemented were not included in this table.

Appendix 4 (continued): Criteria-based analysis of initiatives supporting antibiotic R&D

Initiative	Improves NPV?	Enables participation of SMEs?	Encourages participation of large cap firms?	Facilitates cooperation and synergy?	Promotes antibiotic conservation and patient access?	Targets specific high-priority medical needs?
EU initiatives supporting antibiotic R&D						
• ND4BB: COMBACTE	✔	✖	✔	✔	✖	✔
• ND4BB: COMBACTE-CARE	✔	✖	✔	✔	✖	✔
• ND4BB: COMBACTE-MAGNET	✔	✖	✔	✔	✖	✔
• ND4BB: iABC	✔	✖	✔	✔	✖	✔
• IMI: RAPP-ID	✔	✖	✔	✔	✖	✔
• IMI: PredDiCT-TB	✔	✖	✔	✔	✖	✔
• Better use of Antibiotics Prize	✔	✖	✖	✖	✔	✖
InnovFin ID	✔	✔	✖	✖	✖	✔
EMA	✔	✖	✔	✔	✖	✔

Appendix 4 (continued): Criteria-based analysis of initiatives supporting antibiotic R&D

Initiative	Improves NPV?	Enables participation of SMEs?	Encourages participation of large cap firms?	Facilitates cooperation and synergy?	Promotes antibiotic conservation and patient access?	Targets specific high-priority medical needs?
US initiatives supporting antibiotic R&D						
NIAID/NIH	✔	✔	✔	✔	✖	✔
• AMR Diagnostic Test Challenge	✔	✖	✔	✖	✖	✔
• ARLG	✔	✖	✖	✔	✖	✔
BARDA	✔	✔	✔	✔	✖	?
• BSA Program	✔	✔	✔	✔	✖	?
• BARDA/GSK Partnership	✔	✖	✔	✔	✖	?
• BARDA/AstraZeneca Partnership	✔	✖	✔	✔	✖	?
FDA	✔	✖	✔	✔	✖	✔
GAIN Act	✔	✖	✔	✖	✖	✖

Appendix 4 (continued): Criteria-based analysis of initiatives supporting antibiotic R&D

Initiative	Improves NPV?	Enables participation of SMEs?	Encourages participation of large cap firms?	Facilitates cooperation and synergy?	Promotes antibiotic conservation and patient access?	Targets specific high-priority medical needs?
Canadian initiatives supporting antibiotic R&D						
CIHR-III	✔	✖	✖	✔	✔	?
• NAA Funding Opportunity	✔	✖	✔	✔	✖	✔
• Canada-UK Partnership	✔	✖	✖	✔	✖	✖
Canadian Foundation for Infectious Diseases	✔	✖	✖	✖	✖	?
Canadian Society of Microbiologists	✔	✖	✖	✔	✖	?
UK initiatives supporting antibiotic R&D						
MRC	✔	✖	✖	✔	✖	✖
• UKCRC TIRI	✔	✖	✖	✔	✖	✖
• AMRFF	✔	✖	✖	✔	✖	✖

Appendix 4 (continued): Criteria-based analysis of initiatives supporting antibiotic R&D

Initiative	Improves NPV?	Enables participation of SMEs?	Encourages participation of large cap firms?	Facilitates cooperation and synergy?	Promotes antibiotic conservation and patient access?	Targets specific high-priority medical needs?
UK initiatives supporting antibiotic R&D						
• Tackling AMR – A Cross Council Initiative	✔	✖	✖	✔	✖	✖
• UK-China AMR Partnership Initiative	✔	✖	✖	✔	✔	✔
• UK-India AMR research centres	✔	✖	✖	✔	✔	✔
Longitude Prize	✔	✖	✔	✖	✔	✔
Wellcome Trust	✔	✔	✖	✖	✖	✖
ANTUK	✔	✖	✖	✖	✖	✔
BSAC	✔	✖	✖	✖	✖	✖
Biomedical Catalyst	✔	✔	✖	✖	✖	✖

Appendix 4 (continued): Criteria-based analysis of initiatives supporting antibiotic R&D

Initiative	Improves NPV?	Enables participation of SMEs?	Encourages participation of large cap firms?	Facilitates cooperation and synergy?	Promotes antibiotic conservation and patient access?	Targets specific high-priority medical needs?
French initiatives supporting antibiotic R&D						
ANR	✔	✖	✖	✔	✖	
Inserm	✔	✖	✖	✔	✖	
• Inserm (Transfert)	✔	✔	✖	✔	✖	?
• AVIESAN	✔	✖	✖	✔	✖	?
German initiatives supporting antibiotic R&D						
BMBF	✔	✔	✔	✔	✔	✔
DZIF	✔	✖	✖	✔	✖	✔
InfectControl 2020	✔	✔	✔	✔	✔	?
DFG	✔	✖	✖	✖	✖	✔
Leibniz Institute	✔	✖	✖	✔	✔	?

Appendix 4 (continued): Criteria-based analysis of initiatives supporting antibiotic R&D

Initiative	Improves NPV?	Enables participation of SMEs?	Encourages participation of large cap firms?	Facilitates cooperation and synergy?	Promotes antibiotic conservation and patient access?	Targets specific high-priority medical needs?
Dutch initiatives supporting antibiotic R&D						
Netherlands Center for One Health	✔	✔	✔	✔	✖	✔
ZonMw	✔	?	?	✔	✔	✔
Priority Medicines Antimicrobial Resistance Programme	✔	?	?	✔	✔	✔
Swedish initiatives supporting antibiotic R&D (continued)						
SRC	✔	✖	✖	✔	✖	✔
Vinnova	✔	✔	✖	✔	✖	?
Formas	✔	✖	✖	✔	✖	?

Appendix 5: Incentives employed by initiatives supporting antibiotic R&D

Table Legend: Incentives

Push incentive	DPF	Direct project funding
	RGF	Research grants and fellowships
	RC	Research collaborations
	SR	Sharing R&D resources
	PDP	Product development partnerships
	IC	Investment in R&D capacity
	CN	Collaborative networking
	RS	Risk-sharing financial instruments
Outcome-based pull incentive	EP	End prize/competition
	AMC	Advanced market commitment
Lego-regulatory pull incentive	AA	Accelerated assessment
	MEE	Market exclusivity extensions
	AL	Adaptive licensing
	MAG	Market approval guidance

Note: Initiatives that did not use direct incentives were not included in this table and tabulation of incentives. Moreover, initiatives that have not been fully implemented were not included in this table.

Appendix 5: Incentives employed by initiatives supporting antibiotic R&D

Initiative	DPF	RGF	RC	SR	PDP	IC	CN	RS	EP	AMC	AA	MEE	AL	MAG
International initiatives supporting antibiotic R&D														
JPIAMR	✔		✔				✔							
• 1st Joint Call	✔		✔											
• 2nd Joint Call	✔		✔											
• 3rd Joint Call	✔		✔											
EDCTP	✔	✔	✔	✔	✔	✔								
EU initiatives supporting antibiotic R&D														
EC: DG RTD	✔	✔	✔	✔		✔	✔							
• IMI: ND4BB	✔		✔	✔	✔	✔								
• ND4BB: TRANSLOCATION	✔		✔	✔		✔								
• ND4BB: ENABLE	✔			✔	✔	✔								
• ND4BB: COMBACTE	✔			✔	✔	✔								
• ND4BB: COMBACTE-CARE	✔			✔	✔	✔								

Appendix 5: Incentives employed by initiatives supporting antibiotic R&D

Initiative	DPF	RGF	RC	SR	PDP	IC	CN	RS	EP	AMC	AA	MEE	AL	MAG
EU initiatives supporting antibiotic R&D (continued)														
• ND4BB: COMBACTE-MAGNET	✔			✔	✔	✔								
• ND4BB: iABC					✔									
• IMI: RAPP-ID	✔			✔	✔									
• IMI: PredDiCT-TB	✔			✔	✔									
• Better use of Antibiotics Prize									✔					
InnovFin ID								✔						
EMA											✔	✔	✔	✔
US initiatives supporting antibiotic R&D														
NIAID/NIH	✔	✔		✔		✔	✔							
• AMR Diagnostic Test Challenge									✔					
• ARLG	✔		✔			✔								

Appendix 5: Incentives employed by initiatives supporting antibiotic R&D

Initiative	DPF	RGF	RC	SR	PDP	IC	CN	RS	EP	AMC	AA	MEE	AL	MAG
US initiatives supporting antibiotic R&D (continued)														
BARDA	✔				✔					✔				
• BSA Program	✔				✔									
• BARDA/GSK Partnership			✔		✔									
• BARDA/AstraZeneca Partnership			✔		✔									
FDA											✔	✔	✔	✔
GAIN Act											✔	✔		✔
Canadian initiatives supporting antibiotic R&D														
CIHR-III	✔	✔												
• NAA Funding Opportunity	✔	✔	✔											
• Canada-UK Partnership	✔						✔							
Canadian Foundation for Infectious Diseases		✔												

Appendix 5: Incentives employed by initiatives supporting antibiotic R&D

Initiative	DPF	RGF	RC	SR	PDP	IC	CN	RS	EP	AMC	AA	MEE	AL	MAG
Canadian initiatives supporting antibiotic R&D (continued)														
Canadian Society of Microbiologists		✔												
UK initiatives supporting antibiotic R&D														
MRC	✔	✔	✔				✔							
• UKCRC TIRI		✔	✔											
• AMRFF	✔			✔										
• Tackling AMR – A Cross Council Initiative		✔	✔	✔	✔									
• UK-China AMR Partnership Initiative	✔		✔	✔		✔	✔							
• UK-India AMR research centres	✔		✔	✔		✔	✔							
Longitude Prize									✔					
Wellcome Trust	✔			✔										

Appendix 5: Incentives employed by initiatives supporting antibiotic R&D

Initiative	DPF	RGF	RC	SR	PDP	IC	CN	RS	EP	AMC	AA	MEE	AL	MAG
UK initiatives supporting antibiotic R&D (continued)														
ANTUK	✔													
BSAC		✔												
Biomedical Catalyst		✔												
French initiatives supporting antibiotic R&D														
ANR	✔		✔											
Inserm	✔	✔	✔											
• Inserm (Transfert)			✔	✔										
• AVIESAN	✔	✔	✔											
German initiatives supporting antibiotic R&D														
BMBF	✔	✔	✔											
DZIF	✔		✔											

Appendix 5: Incentives employed by initiatives supporting antibiotic R&D

Initiative	DPF	RGF	RC	SR	PDP	IC	CN	RS	EP	AMC	AA	MEE	AL	MAG
German initiatives supporting antibiotic R&D (continued)														
InfectControl 2020		✔	✔											
DFG	✔		✔											
Leibniz Institute			✔											
Dutch initiatives supporting antibiotic R&D														
Netherlands Center for One Health			✔											
ZonMw	✔													
Priority Medicines Antimicrobial Resistance	✔													
Swedish initiatives supporting antibiotic R&D														
SRC		✔	✔											
Vinnova		✔	✔											
Formas		✔	✔											

Antimicrobial resistance is a global crisis that threatens public health and modern medicine. Discovery and development of novel antibiotic products is a critical component to combating antimicrobial resistance. Numerous initiatives operate at international, European Union and national levels to address the scientific, regulatory and economic barriers to antibiotic innovation.

This study identifies, reviews and critically assesses these initiatives, and ultimately provides a set of policy recommendations for improving the global and European research and development agenda for antibiotics.

"I would like to congratulate Professor Mossialos and his research team at the London School of Economics, the Dutch EU Presidency and the European Observatory on producing an outstanding follow up to the LSE report for the Swedish EU Presidency on the important and topical issue of stimulating research and development for antibiotics. Addressing the challenge of antibiotic resistance is of the highest priority for the Swedish Government at a national, EU and international level."

Gabriel Wikström,
Minister for Health Care, Public Health and Sport, Sweden

Matthew J Renwick, Research Associate in Health Policy and Economics, LSE Health

Victoria Simpkin, Research Associate in Health Policy, LSE Health

Elias Mossialos, Brian Abel-Smith Professor of Health Policy, LSE; Professor of Health Policy and Management, Institute of Global Health Innovation, Imperial College London; Co-Director, European Observatory on Health Systems and Policies

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